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A THERMAL MODEL COMPARISON STUDY.(U)
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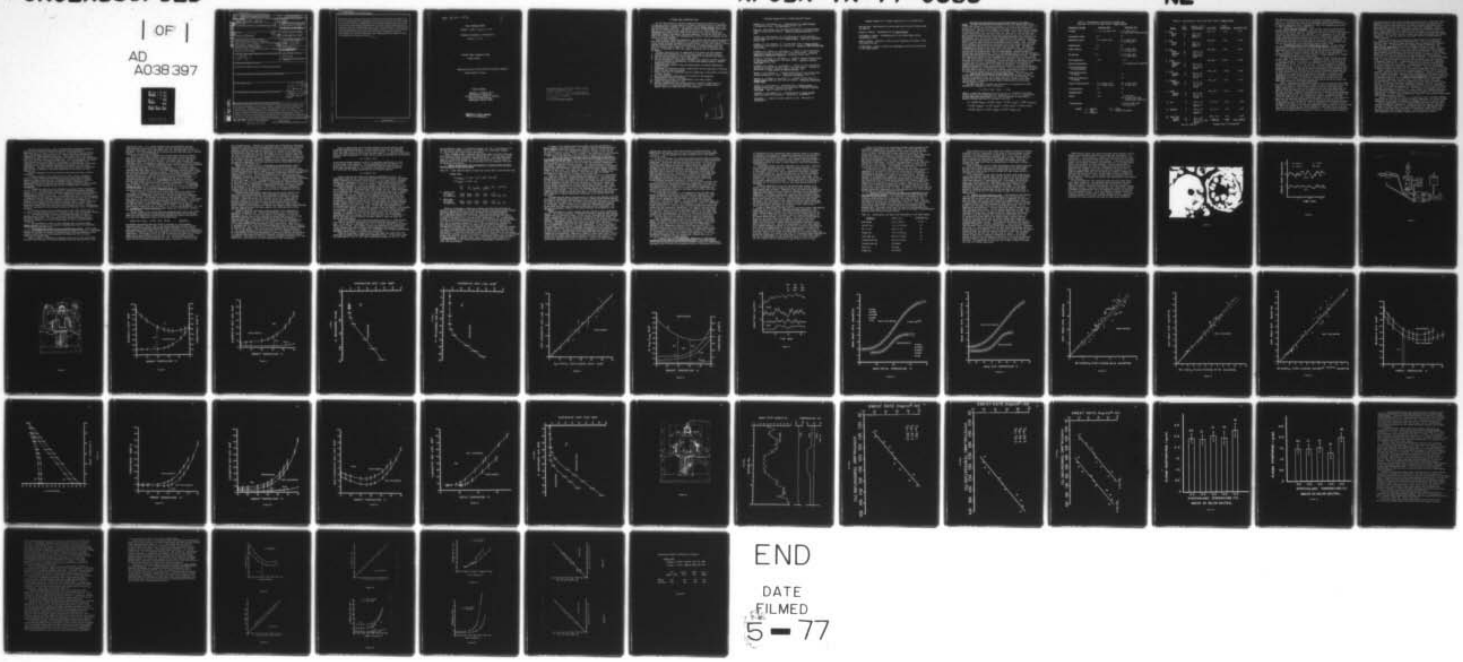

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The major findings of this work revealed the histology and histochemistry of eccrine sweat glands in the rhesus monkey, together with their density and distribution. Although not as highly vascularized as those in man, their relative density and distribution is comparable to man's. As in man, it also appears that the sweating response is intermittent in nature, due to either a cycling of the nervous impulses to the glands or to the intermittent expulsion of sweat onto the skin surface. Measured metabolic, respiratory, vasomotor and →

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20. sudomotor effector responses all indicate that the rhesus monkey can serve as an adequate thermoregulatory model for experiments which cannot be performed on man. Additionally, these findings support the concept that control body temperature (hypothalamic and skin) interact additively in the control of rhesus sweating. Because of the close proximation of hematocrit, and total body water (intra and extracellular) to those of man, cold and heat acclimatized monkeys may well serve as useful surrogates of man in determining the role that body fluid shifts might play in the ability to adapt to various types of thermal stress.

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FINAL TECHNICAL REPORT

January 1, 1973 - January 31, 1977

Prepared by Reynaldo S. Elizondo Ph.D.

January 31, 1977

A Thermal Model Comparison Study

AFOSR 73-2473

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United States Air Force

Project Manager

Reynaldo S. Elizondo, Ph.D.
Department of Physiology
Indiana University School of Medicine
Medical Sciences Program
Bloomington, Indiana 47401

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A THERMAL MODEL COMPARISON STUDY

The Air Force Office of Scientific Research through grant #73-2473 has, over a three year period, provided support for research designed primarily to quantitate the thermoregulatory responses of the subhuman primate Macaca mulatta under a wide specturm of thermal conditions. The adaptive capacity of this primate to prolonged heat and cold exposure has been examined and its use as a viable model for thermoregulatory studies which cannot be performed in man, such as hypothalamic temperature clamping experiments, have been evaluated. During the final year, the grant also provided support for thermoregulatory studies in man with emphasis on the control of eccrine sweating.

Interim reports summarizing progress on the project have been submitted annually. This final technical report therefore, will summarize the major scientific findings of the studies performed throughout the project period. It will not, however, include complete thermal balance data collected from cold acclimated monkeys toward the end of the project period (August 31, 1976) which is currently undergoing final analysis. A suppliment to this final report, therefore, will be submitted within six months.

The major areas which will be summarized in this report are the following:

1. Histology and histochemistry of eccrine sweat glands in the rhesus monkey.
2. Density and distribution of eccrine sweat glands on the general body surface.
3. Eccrine sweating responses of the rhesus monkey.
4. The role of metabolic, respiratory, vasomotor, and sudomotor effector responses in the maintenance of thermobalance in unacclimated monkey exposed to ambient temperature from 15-45°C.
5. Thermoregulatory profile of heat acclimated monkeys at ambient temperatures between 15-45°C.
6. Development of predictable control systems models for the regulation of sweating before and after heat acclimation.
7. Study of the role of hypothalamic and skin temperature in the control of sweating in higher primates.
8. Role of hypothalamic temperature in the control of the sympathico-adrenomedullary system in primates.
9. Cardiovascular and body fluid compartments in the rhesus monkey.
10. Control of palmar sweating in man.
11. Complete thermobalance data and development of controls systems models for the regulation of sweating and metabolic rate in cold acclimated rhesus monkeys (data to be submitted after final analysis).

Published Communications of AFOSR Supported Research

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Elizondo, R., and Johnson, G.S. Thermoregulation in Macaca mulatta before and after cold acclimation. Manuscript in preparation.

Robertshaw, D. Control of palmar sweating in man. (Manuscript in preparation.)

Graduate Student Ph.D. Projects Supported In Part By AFOSR Funds

Wen Juan Chen. Modification of eccrine sweat gland function following heat acclimation.

George S. Johnson. Thermoregulation in Macaca mulatta.

Christopher C. Barney. Thermoregulation in the rhesus monkey during prostoglandin fever.

Bruce A. Martin. Influence of diet on use of substrate for energy in long-term exhausting work.

Ib Oddershede. Changes in body fluid compartments during heat acclimation in the rhesus monkey.

1. Histology and histochemistry of eccrine sweat gland in the rhesus monkey. The basic histology of eccrine sweat glands on the general body surface of the rhesus monkey is illustrated in Figure 1. It shows cross-sections of the secretory coil on the left and the excretory duct both of which are stained with toluidine blue. Note that the secretory coil consists of a single layer of columnar or pyramidal-shaped cells of two different cell types: smaller ones crowded near the luminal border which stain with basic dyes, the "dark cells", and the larger cells near the basement membrane which stain poorly with basic dyes, the "clear cells". Myoepithelial cells are situated inside the basement membrane of the secretory coil. The excretory ducts of the eccrine sweat gland consist of two layers of strongly basophilic cells; myoepithelial cells are absent in the excretory duct. The luminal cells of the duct have a variably, keratinized cuticular border. Table I outlines the histochemical distribution and localization of various enzymes and substrates which have been identified within the rhesus eccrine sweat gland. Glycogen is predominantly localized in the clear cells of the secretory coil, and is present in trace amounts throughout the outer cells of the duct. The gland is strongly reactive for cytochrome oxidase, succinic dehydrogenase, monoamine oxidase, B-glucuronidase and phosphorylase. There is only moderate activity for the esterases, and only the intercellular canaliculi show alkaline phosphatase activity. In addition, the intercellular canaliculi and the membranes of the clear cells of the secretory coil show strong ATP-ase activity; whereas, the cytoplasm of the dark cells in the secreotry coil contain 5 nucleotidase. The eccrine glands of the rhesus are surrounded by nerves that are rich in acetylcholinesterase and butyrylcholinesterase which suggests that the innervation of the glands is cholinergic. The reaction of butyrylcholinesterase is much stronger than the reaction of acetylcholinesterase; and both reactions can be abolished with eserine. The eccrine glands are surrounded by blood vessels which are reactive for alkaline phosphatase and ATP-ase, however, the glands do not appear to be as highly vascularized as those in man.

2. Density and distribution of eccrine sweat glands. Table II shows that in the rhesus active eccrine glands are most numerous on the palms and soles, and then in decreasing order, on the head, the trunk, and the extremities. This relative distribution and the mean weighted density of glands in the rhesus (120 gland/cm^2) is comparable to the relative distribution and the average density reported in man.

The data from Table II permits the derivation of an expression for mean weighted skin temperature which is defined as:

$$T_s = S_1T_1 + S_2T_2 + S_3S_4 \ldots + S_nT_n$$

where T_s = mean skin temperature (°C); S_1, S_2, S_3, S_n = percent of total body surface area from which temperature was measured; T_1, T_2, T_3, T_n = regional skin surface temperature measurements (°C). Thus an equation for calculating T_s based on ten body positions for the monkey would be:

$$T_s = (0.054)\,(T_{hand}) + (0.085)\,(T_{foot}) + (0.139)\,(T_{head}) + (0.082)\,(T_{forearm})$$
$$+ (0.122)\,(T_{chest}) + (0.127)\,(T_{back}) + (0.103)\,(T_{calf}) + (0.032)\,(T_{tail})$$
$$+ (0.162)\,(T_{tail}) + (0.162)\,(T_{thigh}) + (0.093)\,(T_{upper\ arm}).$$

Table 1. Histochemical Localization of Enzymes and Substrates in the Eccrine Sweat Gland of Macaca mulatta

Substrate or Enzyme	Excretory Duct	Secretory Coil
Glycogen	* - to + in basal cells	++ in clear cells + in dark cells (SPDR granules)
Cytochrome oxidase	+++	+++
Monoamine oxidase	+++ in basal cells	+++ in clear cells ++ in dark cells
Phosphorylase	+++	+++
Tween esterase	* ++	* ++ in dark cells * + in clear cells
AS esterase	* ++	* ++ in dark cells + in clear cells
Acid phosphatase	- to +	- to +
Alkaline phosphatase	-	+ in intercellular canaliculi
Alkaline phosphatase in blood vessels	-	+
Acetylcholinesterase in nerves	-	++
Butyrylcholinesterase in nerves	-	+++
Succinic dehydrogenase	+++ in basal cells ++ in luminal cells	+++ in clear cells ++ in dark cells
B-Glucuronidase	+++	+++
Aminopeptidase	- to +	++
ATPase	- to +	- in dark cells +++ in clear cells and intercellular canaliculi
5-Nucleotidase	-	++ only in dark cells - in clear cells

LEGEND:
- : negative
+ : weak
++ : moderate
+++ : strong
* : regional variations

Table II. Distribution of the Eccrine Sweat Gland in Macaca mulatta

Region	# of Cases	Density ± S.E.M. (glands/cm^2)	Area (cm^2)	% Body Surface Area	per Area x 10^{-3}
1. Hand			153 ± 9.9	5.4%	61.35
Dorsal	8	112 ± 5.8			
Palm	6	690 ± 47			
		(401)			
2. Foot			242 ±18.3	8.5%	87.36
Dorsal	9	133 ± 7.2			
Sole	6	589 ± 70			
		(361)			
3. Head			395 ±18.4	13.9%	34.21
Cheek	10	58.5 ± 1.3			
Forehead	9	110.7 ± 2.0			
Scalp	7	76.6 ± 1.7			
		(8.6)			
4. Trunk			709 ±20.2	24.9%	59.49
Chest and Abdomen	11	70.5 ± 3.4			
Back	9	97.2 ± 2.8			
		(83.9)			
5. Calf			291 ± 26.1	10.3%	23.60
Lateral	8	96.8 ± 1.8			
Medial	9	65.3 ± 3.5			
		(81.1)			
6. Forearm			234 ± 15.7	8.2%	17.55
Extensor	9	77.7 ± 3.3			
Flexor	9	72.3 ± 2.0			
		(75.0)			
7. Thigh			401 ± 28.3	14.1%	29.99
Lateral	9	85.3 ± 2.8			
Medial	8	64.3 ± 1.6			
		(74.8)			
8. Tail	8	69.0 ± 2.4	91 ± 5.6	3.2%	6.28
		(69.0)			
9. Buttocks	8	66.8 ± 2.4	60 ± 5.3	2.1%	4.01
		(66.8)			
10. Upper Arm			265 ± 12.5	9.3%	16.09
Lateral	10	83.3 ± 2.5			
Medial	10	38.1 ± 0.8	Avg: 2841 cm^2	100%	TOTAL: 339.93
		(60.7)			

Avg. Wt. 3.26 kg.

Weighted mean: 120 glands/cm^2

This ten-point method was evaluated over an ambient temperature range of 15-45°C. It was found that inner thigh temperature correlated extremely well with Ts (R = 0.99) with the mean absolute difference being 0.20°C over the range of ambient temperatures used. Consequently, inner thigh temperature was used in these experiments as a measurement of Ts.

3. Eccrine sweating responses. Figure 2 shows a typical sweating record obtained from a non-heat acclimated animal after two hours of heat exposure at 41.8°C and 20% relative humidity. The sweating rate on the palm was 9.96 mg/cm^2/hr and that on the lateral calf 4.47 mg/cm^2/hr. It is noteworthy, as is the case in man, that both sweating records are cyclical in nature which indicates that either intermittent nervous impulses are arriving at the glands, and/or that the mechanism for the expulsion of sweat onto the skin surface is intermittent. It is also significant that the two patterns are synchronous, which indicates that they are both regulated by the same central neural control system.

4. Thermobalance study of unacclimated Macaca mulatta. The next phase of the study involved construction of a complete thermoregulatory profile of the rhesus monkey in order to evaluate and quantify the relative significance of evaporative heat losses due to eccrine sweating and respiratory evaporative water loss. In addition, particular emphasis has been placed on the quantitation of the physiological control of eccrine sweating in Macaca mulatta and to compare its thermodynamic properties with those of man.

Six young male rhesus monkeys weighing between 3.09 and 3.70 kgm were used in this study. They were maintained in a temperature chamber controlled at 25 $\pm$ 1°C and were trained to sit quietly in a restraining chair for the duration of an experimental period. Each animal had a minimum of two exposures to ambient temperatures of 15, 20, 25, 30, 35, and 40°C. Relative humidity was controlled at each temperature to $\pm$ 5% in order to insure equivalent thermal stress on each subsequent exposure. No food was allowed on the morning of the experimental day. An animal was allowed to equilibrate at any given environmental temperature for at least two hours in the cold and one and one-half hours in the heat in order to assure that a steady state was achieved as indicated by: constant oxygen consumption and carbon dioxide production and variations in rectal and skin temperatures of less than $\pm$ 0.10°C over a fifteen minute period prior to an experimental run. Each experimental period consisted of two thirty minute runs after equilibration at each ambient temperature.

Figure 3 represents the experimental setup in which an open-flow draw system was used for continuous measurements of metabolic rate and respiratory water loss. Room air was drawn at a constant rate through a hood over the animal's head. Oxygen consumption and carbon dioxide production was calculated downstream, and total air flow was measured using rotometers which had been calibrated using a wet test flow meter. Metabolic heat production was calculated from O_2 consumption, CO_2 production and from directly determined RQ values. In these experiments, the average RQ value was 0.86. The combined heat transfer coefficient averaged 5.79 $\pm$ 0.7 W/M^{2}C over the ambient temperature range of 15-40°C. Total evaporative water loss was monitored continuously by mounting the restraining chair on a Potter balance. As illustrated in Figure 4, respiratory water loss was monitored by employing two pairs of wet bulb - dry bulb thermistors. The first pair was situated in the inflow to the hood and recorded the absolute humidity of the inspired air, while the second pair was located immediately downstream from the hood and monitored the absolute humidity of the expired air. Thus respiratory evaporative water loss was determined by subtraction of the first value of absolute humidity

from the second since the airflow through the hood was known. Since inner thigh temperature showed a strong positive correlation with mean skin temperature as measured by the ten point method over the range of ambient temperatures used in these experiments, it was used as an index of mean skin temperature. Rectal temperature was measured with a thermistor inserted ten centimeters beyond the anus. Rectal temperature was maintained within the range of 37.7 to 39.6°C at ambient temperatures from 15 to 40°C; mean skin temperature was maintained within the range of 28.9 to 39.9°C and had a significant linear relationship with ambient temperature. All data was sampled at ten second intervals and manipulated on a PDP-12 computer.

Figure 5 illustrates the relationship between metabolic heat production (M), conductance (K), and ambient temperature (Ta). There is a significant negative linear correlation between decreasing ambient temperature and metabolic rate below 28°C. As determined by the intercept method of Scholander, the lower critical temperature (LCT) for the increase in metabolic heat is 25°C. This LCT represents the lower limit of the thermal neutral zone (TNZ). Recently, Wilkerson et al. have shown that the lower critical temperature in unacclimated male caucasians as determined by the intercept method is 25.2°C. In the rhesus monkey, the critical skin temperature for the increase in metabolic rate is 33.5°C. At a Ta of 15°C, frank shivering was occasionally apparent. At temperatures above 28°C, M was fairly constant with a value of 51 W/M^2. In the 15°C environment M was 1.7 times the metabolic rate in the TNZ: Wilkerson et al. have reported a comparable change in man. At temperatures below the LCT of 25°C, conductance (K) has a minimum value of 10 W/M^2 - C indicating that maximal vasoconstriction is in effect below this temperature. At temperatures above 25°C, conductance gradually increased to a value of 54 W/M^2 - C at 40°C. This five fold increase is similar to that observed for man in the ambient temperature range of 20 to 48°C.

Figure 6 depicts the relationship between evaporative heat loss due to eccrine sweating, respiratory water loss and ambient temperature. There is a significant linear correlation between increasing ambient temperature and evaporative heat loss due to sweating above 30°C. The upper critical temperature (UCT) for the increase in evaporative heat loss due to sweating as determined by the intercept method is 30.8°C, which represents the upper limit of the thermal neutral zone (TNZ). The corresponding critical mean skin temperature for the onset of sweating is 35.17°C. It should be noted that respiratory evaporative heat loss is relatively constant over the range of ambient temperatures studied. At 15°C, respiratory heat loss is 3.2 W/M^2 and decreases to a minimum of 2.3 W/M^2 in the TNZ, and then gradually increases to 4.9 W/M^2 at 40°C. The increase in respiratory heat loss with decreasing ambient temperature is probably due to the increased respiratory function which accompanies the increase in oxygen consumption at lower ambient temperatures. At higher ambient temperatures respiratory rate increased approximately 20%, but panting was not observed.

Figure 7 illustrates that there is a significant linear correlation between evaporative heat loss due to sweating and rectal temperature. The value of rectal temperature for the onset of sweating is estimated to be 38.17°C from our data.

Figure 8 demonstrates the relationship between evaporative heat loss due to sweating and mean skin temperature. Evaporative heat loss remains relatively constant at minimal levels over a wide range of mean skin temperatures from 30 to 34°C; on the other hand, when mean skin temperature reaches 35-36°C, the evaporative heat loss increases rapidly. From these data the value of mean skin temperature for the onset of sweating is estimated to be 35.17°C.

The next figure (9) shows a plot of experimentally determined evaporative heat loss versus predicted evaporative heat loss calculated from an expression $E_{sw} = 9.01 (Tre - 38.17) + 5.26 (\bar{T}_s - 35.17)$ W/M^2 which was derived from a two parameter regression analysis of rectal temperature and mean skin temperature on sweat evaporative heat loss. The diagonal line is the line of equality which would result if the combination of rectal and mean skin temperatures were exact predictors of evaporative heat loss. For a resting monkey in a steady state the data points distribute well with respect to the predicted line. Consequently, the observed changes in steady state evaporative heat loss are well correlated with a linear additive combination of both mean skin and rectal temperatures. These data indicate that the physiological control of evaporative heat loss due to sweating in the rhesus monkey may be very similar to that found in man.

Figure 10 summarizes the major findings of the study which may be stated as follows:

1. Resting metabolic heat production has a lower critical temperature (LCT) of 25.02°C; below this temperature the rhesus cannot maintain thermal balance by reducing heat losses and consequently heat production is elevated. This is supported by the fact that conductance reaches a minimum in this temperature range which indicates that maximum vasoconstriction has been achieved. The increase in heat production below the LCT is probably due to shivering thermogenesis.

2. Evaporative heat loss due to sweating has an upper critical temperature (UCT) of 30.8°C. At temperatures above 38.3°C, although conductance increases rapidly, it is insufficient alone to maintain thermal balance and eccrine sweating becomes the main avenue of heat loss. It is interesting to note the relative insignificance of the slight increase of respiratory heat loss in a hot environment in comparison with the tremendous increase in evaporative heat loss due to sweating above the UCT. Panting was never observed in these animals although a 20% increase in respiratory rate above neutral levels was noted. At 40°C evaporative heat loss due to sweating can dissipate approximately 94% of metabolic heat production, whereas respiratory heat loss could dissipate only 9.6%. Consequently, it must be concluded that eccrine sweating serves as the major source of evaporative heat loss.

3. The data indicate that the thermal neutral zone (TNZ) extends from 25 to 30.8°C, and that thermoregulation is achieved in this region by vasomotor control.

4. The observed changes in steady state evaporative heat loss due to sweating are well correlated with a linear additive combination of mean skin and rectal temperatures. Thus the physiological control of evaporative heat loss due to sweating in the resting rhesus monkey is similar to that found in resting man.

5. The experimental evidence to date indicates that the rhesus monkey (Macaca mulatta) can serve as an adequate thermoregulatory model for experiments which cannot be performed on man.

5. Thermoregulatory profile of heat acclimated rhesus monkey. Another major area of investigation during the grant period has consisted of a series of experiments designed to elucidate the changes in thermoregulatory effector mechanisms induced by heat acclimatization and the development of appropriate control systems models for the rhesus monkey.

Figure 11 depicts a comparison of sweating rates from the same animal before and after thirty-two days of heat-acclimatization obtained under essentially the

same thermal drive. It is readily apparent after acclimatization that the sweating rates on the palm and the lateral calf have increased significantly. During the same period, total evaporatory water loss increased from 7.76 to 11.12 $mg/cm^2/hr$. It is also noteworthy, as is the case in man, that both sets of sweating records are cyclical and synchronous.

Figure 12 illustrates a composite plot of mean sweat rate on the lateral calf for six animals before and after heat acclimatization, versus mean rectal temperature which was constructed by plotting mean sweat rate as a function of mean rectal temperature in 0.1°C intervals. The dashed lines represent 95% confidence limits. An exponential equation which is asymptotic to maximum evaporative water loss and to insensible evaporative water loss was found to be an excellent fit to both sets of data and has the following form: $Y = K(1-ae^{-bxm})$, where Y is the mean sweat rate, x is the rectal temperature, K is the upper asymptote (maximum evaporative water loss), C is the lower asymptote (insensible water loss), and b and m are empirically derived constants. These models are analogous to those for the sweat rate/rectal temperature relationship described by Wyndham for man. From this figure, it is clear that the curve for the acclimatized monkeys is significantly different from that of the unacclimatized (at the .05 level). In the heat acclimatized state: (1) the threshold for the onset of sweating is shifted significantly (at the .01 level) to the left from 37.65 to 37.20°C; (2) the gain of the sweat rate/rectal temperature relationship is significantly greater (at the .01 level), i.e., 0.87 to 1.35 $mg \cdot cm^2\ hr^{-1} \cdot °C^{-1}$; (3) insensible evaporative water loss is significantly increased (at the .05 level), i.e., 1.36 to 1.91 $mg/cm^2/hr$; and (4) maximum evaporative water loss is also significantly increased (at the .05 level), i.e., 4.09 to 9.06 $mg/cm^2/hr$.

Figure 13 depicts a composite plot of mean sweat rate on the lateral calf versus mean skin temperature for both control and heat-acclimatized states (constructed by plotting mean sweat rate as a function of mean skin temperature in 0.1°C intervals). The dashed line represents 95% confidence limits. From this figure, it is clear that the curve for the acclimatized monkeys is significantly different from that of the unacclimatized monkeys (at the .05 level). In the heat acclimatized state: (1) the threshold is shifted significantly to the left (by .44°C at the .01 level), i.e., from 35.40 to 34.96°C; (2) the gain is significantly increased (at the .01 level), i.e., 0.49 to 0.58 $mg \cdot cm^{-2} \cdot hr^{-1} \cdot °C^{-1}$; and (3) insensible and maximum evaporative water losses are significantly increased (at the .05 level).

Figure 14 shows a plot of experimentally determined sweat rate on the lateral calf for the pooled data of the non-heat acclimatized animals versus predicted sweat rate calculated from an additive model representing central drive modified by a local skin temperature factor in the following form:

$$\text{Sweat rate} = a(T_{rec} - 37.65) + B(T_s - 35.40) \qquad (mg/cm^2/hr)$$

The theraml and sweating data were fitted to the model by a two-parameter regression analysis. Where, 0.865 is the rectal proportional control constant, 0.491 is the skin temperature proportional control constant, T_{sl} is the local skin temperature of the lateral calf, and 37.65°C and 35.40°C are the experimentally determined thresholds for the onset of sweating for rectal and mean skin temperatures respectively. The diagonal line is the line of equality which would result if the model were an exact predictor of sweat rate. For a resting monkey, the data points distribute well with respect to this line. The relative weighting of the rectal to the skin temperature proportional control constants is 1.77:1 for the

non-acclimated rhesus. Although this experiment was not designed to investigate the possible role of the local skin temperature effect in the control of eccrine sweating, incorporation of the multiplicative term significantly improved the predictive ability of the modes as indicated by an increase in the coefficient of determination from 0.90 for the linear model to 0.96 for the non-linear mode. The local skin temperature constant was estimated using an iterative method of non-linear regression analysis. The standard error of the estimate of sweat rate on the lateral calf over the ranges indicated in this figure is $\pm$ 0.32 mg/cm^2/hr. All F values in the above regression indicate that both rectal temperature (T_{re}) and mean skin temperature (T_s) play significant roles in determining the level of sweating on the lateral calf.

Figure 15 illustrates a plot of experimentally determined sweat rate on the lateral calf of the pooled data of the heat-acclimatized animals versus preducted sweat rate derived from regression analysis as in the previous figure. The rectal proportional control constant is 1.35 and the skin temperature proportional control constant is 1.35 and the skin temperature proportional control constant is 0.580 mg$\cdot$cm^{-2}.hr$^{-1}\cdot$°C^{-1}. The relative weighting of the internal to the skin temperature proportional control constants is 2.33:1 in the acclimatized animals as compared to 1.77:1 for the non-acclimatized animals. The coefficient of determination for this model is 0.90. The standard error of the estimate of sweat rate on the lateral calf is $\pm$ 0.30 mg/cm^2/hr. Incorporation of a multiplicative term as shown in Figure 16 significantly improved the predictive ability as indicated by an increase in the coefficient of determination to 0.95; the standard error of the estimate is $\pm$ 0.34 mg/cm^2/hr. All F values in the above regressions indicate that both T_{re} and T_s play significant roles in determining the level of sweating on the lateral calf.

Pharmacological observations demonstrate that the eccrine glands of the rhesus can be stimulated maximally with subcutaneous injection (0.1 ml) of mecholyl (5 mg%) which in turn can be blocked with an injection of atropine (0.5 mg%). Butyrylthiocholine (1.0 mg%) was found to also induce sweating activity, however, not to the degree elicited by the same concentration of mecholyl; prostigmine (0.2 mg%) was found to enhance the activity of both hutyrylthiocholine and mecholyl. Epinephrine (0.1 mg%) was found to have no effect; isotonic saline injected as a control also showed no effect which indicated that any trama which might have been caused by the injections had no effect upon the sweating rates.

Figure 17 shows the relationship between metabolic heat production (M) and ambient temperature (Ta). After heat acclimation, (M) is significantly depressed ($p < .05$) by 17.1% over the range of Ta's employed. On this and subsequent figures, open circles represent the unacclimated state, and X's the heat acclimated state; each symbol represents the mean of four animals $\pm$ 2 standard deviations. As determined by the intercept method of Scholander, the lower critical temperatures (LCT) for the increase in M are 24.7 and 25.6°C for the unacclimated and heat-acclimated states, respectively. Above the LCT M, decreased from 51.1 to 42.6 W/m^2 after acclimation; below the LCT, M increased so progressively that at 15°C it was 1.81 x TNZ values after acclimation compared to 1.73 x's for control. There are significant negative linear correlations ($p < .05$) between decreasing Ta and M below the LCT. This apparent increase in M is attributable to shivering thermogenesis; according to Chaffee, the depression in M observed after heat acclimation is secondary to metabolic chemical thermo-suppression. The critical Ts and T_{rec} at the LCT decreased significantly ($p < .05$) from 33.5 to 32.6°C and 38.1 to 37.6°C respectively, after acclimation.

Figure 18 demonstrates the relationship between Tre and Ts over the range of ambient temperatures employed. In unacclimated animals The was maintained within the range of 37.9 to 40.0°C at Ta's from 15 to 40°C. Ts was maintained within the range of 29.9 to 39.3°C over the same range of Ta's, and has a significant positive linear correlation (R = 0.98) with Ta, and may be expressed by the following equation:

$$Ts = 0.40Ta + 23.3$$

In the heat acclimated animals The and Ts is depressed significantly ($p < .05$) over the range of Ta's employed. The was maintained within the range of 37.4 to 40.6 at Ta's from 15-45°C. Ts was maintained within the range of 28.4 to 40.4°C over the same range of Ta's, and has a significant linear correlation (R = 0.97) with Ta, and may be expressed by the following equation.

$$Ts = 0.42Ta + 21.7$$

Figure 19 depicts the relationship between conductance (K) and Ta. At temperatures below the LCT, K had a minimum value of 8.85 for the heat -acclimated animals compared to 10.83 $W/(m^2 \cdot °C)$ for control. At Ta's above 25°C, K increased gradually to a maximum of 73.6 at 45°C for the heat-acclimated animals compared to a maximum of51 $W/(m^2 \cdot °C)$ at 40°C for control. After heat-acclimation, K is significantly depressed ($p < .05$) by an average of 27% over the range of Ta's used.

Figure 20 depicts the relationship between evaporative heat losses due to eccrine sweating (Esw), respiratory water loss (Eresp), and Ta. After acclimation, Esw is depressed significantly ($p < .05$) by 19.8%, over the range of Ta's, secondary to the decrease in M. As determined by the intercept method, the upper critical temperature (UCT) for the increase in Esw increased from 30.6 to 31.4°C after acclimation. Consequently, after heat acclimation the thermoneutral zone (TNZ) shifted upward significantly from 24.7 to 30.6°C for control to 25.6 to 31.4°C. In addition, it should be noted that after heat acclimation the rhesus monkey can maintain thermal balance at 45°C; whereas, an unacclimated animal cannot maintain thermal balance at Ta's above 40°C. This indicates that heat acclimation leads to increased heat tolerance in the rhesus. In the TNZ, Eins decreased from 12.8 to 8.8 W/m^2; however, increased heat tolerance after acclimation is attributable to an increase in maximum Esw from 51 to 84 W/m^2. It should be noted that Eresp is relatively constant and insignificant relative to Esw over the range of Ta's employed. For example, at 40°C, for the control animals, Esw can dissipate approximately 99% of M, whereas Eresp can dissipate only 9.1%! Consequently, it must be concluded that Esw serves as the major avenue of heat loss above the UCT in the rhesus monkey.

Figure 21 illustrates the relationship between Eresp and Ta. After acclimation Eresp is depressed significantly ($p<.05$) by 28.5% over the range of Ta's used. In the TNZ, it is decreased from 2.33 to 1.44 W/m^2; maximum Eresp increases from 4.8 to 7.1 W/m^2. The increase in Eresp with decreasing Ta is probably due to the increased respiratory function which accompanies the increase in oxygen consumption at lower Ta's. At higher Ta's, respiratory rate increased approximately 20% above neutral values, but panting was not observed.

Figure 22 illustrates a composite plot of mean sweat rate (Esw) before and after heat acclimation versus mean rectal temperature (Tre). In both cases, there are significant (R = 96; R = 98) linear correlations between Esw and Tre. After

heat acclimation, there is a significant decrease ($p < .05$) in the threshold Tre for the onset of sweating from 38.17 to 37.82°C, and a significant increase ($p < .05$) in the gain of the Esw/Tre relationship.

Figure 23 demonstrates a composite plot of mean sweat rate (Esw) before and after heat acclimation versus mean skin temperature (Ts). In both cases, there is a significant linear correlation between Esw and Ts. After heat acclimation, there is a significant decrease ($p < .05$) in the threshold Ts for the onset of sweating from 35.17 to 34.24°C, and a significant ($p < .05$) increase in the gain of the Esw/Ts relationship.

6. Control systems models for the regulation of sweating before and after heat acclimation in the rhesus monkey.

Table III. Linear additive models of sweat rate on the lateral calf and whole body

GENERAL FORM:

$$S.R._{(UNACCL)} = a\,(Tre - Tre_o) + B(\bar{Ts} - \bar{Ts}_o)\ W/m^2$$

$$S.R.^{1}_{(ACCL)} = a'(Tre - Tre$$

	Tre (°)	$\bar{Ts}$ (°)	a' ($W/m^2°C$)	B' ($W/m^2°C$)	a/B	a'/a	B'/B
1. Lateral Calf:							
(a) Unaccl.	37.65	35.40	6.26	3.53	1.77	-	-
(b) Heat-Accl.	37.20	34.44	9.71	4.17	2.33	1.55	1.18
2. Whole Body:							
(a) Unaccl.	38.17	35.17	9.01	5.26	1.71	-	-
(b) Heat-Accl.	37.82	34.24	15.25	6.68	2.28	1.69	1.27

Table III illustrates a comparison of models describing the physiological control of eccrine sweating on the whole body (derived from thermal balance studies) and local sweating of the lateral calf (derived from resistance hygrometry) before and after resting heat-acclimation. After heat-acclimation there is: (1) a significant decrease ($p < .01$) in the thresholds for the onset of sweating in terms of Tre and Ts (i.e., 0.35 and 0.96°C, respectively); (2) a significant increase in the relative weighting of the Tre and Ts proportional control constants, i.e., a/B of 1.71 to 2.28 for the whole body and 1.77 to 2.33 for the lateral calf; (3) a significant increase ($p < .01$) in the Tre proportional constants for both the whole body and lateral calf models with the relative increases as indicated by a'/a being 1.69 and 1.55, respectively; and, (4) a significant increase ($p < .01$) in the proportional control constants for both the whole body and lateral calf models with the relative increases as indicated by B'/B being 1.27 and 1.18, respectively. It should be noted that in both sets of models after heat-acclimation the relative increases in the Tre proportional control constants, a'/a, are significantly greater than those for the mean skin, B'/B. Consequently, resting heat acclimation in Macaca mulatta, in contrast to man, results in a significant increase in the input from the core to the central controller (hypothalamus) relative to the input from the periphery.

In summary, this thermal balance data suggest that heat acclimation in Macaca mulatta is characterized by: (1) metabolic chemical thermalsuppression, (2) an upward shift in the thermalneutral zone LCT from 24.7 to 25,6 and the UCT from 30.6 to 31.4; (3) a decrease in threshold, increase in gain, and an increase in sweating capacity, (4) an increase in the sensitivity of the regulation of sweat rate by the controller, (5) an increase in maximal heat tolerance.

7. Study of the role of hypothalamic and skin temperature in the control of sweating in higher primates. The other major area of research activity undertaken during the current support period was a series of hypothalamic perfusion studies designed to elucidate the role of central and peripheral temperatures in the control of sweating in higher primates. The interrelationships between hypothalamic temperature, skin temperatures, and sweating activity on the general body surface were evaluated on four male unanesthetized rhesus monkeys weighing between 5.8 and 7.2 kg. The animals were housed in a climatic chamger controlled at 34 + 1°C with 30% relative humidity, given food and water ad libitum, and maintained on a light cycle of 12 hours on and 12 hours off.

Figure 24 illustrates the experimental techniques utilized to study general body sweating at different clamped hypothalamic temperatures. The animals were trained to sit quietly in a restraining chair maintained in a climatic chamber for the duration of an experimental session which lasted from two to three hours. The two chambered circulator which was individually fitted to each animal was used to perfuse the chronically implanted hypothalamic thermodes. Water from a Lauda constant temperature circulating bath was pumped into the upper chamber and then directly to the closed tip of the thermodes through small 22 gauge stainless steel catheters. The outflow from the thermodes passed into the bottom chamber and back to the circulating water bath. This perfusion system proved very effective in clamping hypothalamic temperature at any desired level from 36 to 40°C.

The magnitude and dynamic characteristics of general body sweating associated with specific hypothalamic temperatures (36-40°C) clamped and maintained constant for three to five minutes were continuously monitored from small areas on the palms (2.75 cm^2) and the lateral calf (9.0 cm^2) using resistance hygrometry capsules as illustrated. Rectal, lateral calf, and mean skin temperature as measured on the inner thigh were also continuously monitored with USI thermistors. All data were continuously sampled at five second intervals and analyzed on a PDP-12 computer.

Figure 25 depicts a typical sweating response induced by local hypothalamic cooling. The figure illustrates a continuous recording of sweating rate from the lateral calf as a function of time. At the top are illustrated the corresponding rectal, hypothalamic, and skin temperature as measured on the inner thigh. The animal had been allowed to equilibrate for one hour at 38.5°C and 20% relative humidity. Consequently, during the initial five minute control period illustrated, all of the recorded temperatures were stable and averaged 39.1 for rectal, 38.8 for hypothalamic, and 37.5°C for skin temperature. On the fifth minute of the experiment, the hypothalamic thermodes were perfused with 35°C water which produced a significant drop in hypothalamic temperature from the controlled level of 38.8 to 38.5°C. The decreased hypothalamic temperature was maintained fairly constant until the eleventh minute of the experiment when the perfusion was stopped and the hypothalamic temperature allowed to return toward control levels. During the five minute control period sweating activity on the lateral calf was cyclical and averaged approximately 6/mg/cm^2.hr. Following the decrease in hypothalamic temperature and with no significant change in any other recorded

temperatures, there was a significant decrease in sweating activity. The sweating activity remained cyclical but at a reduced level of approximately 3 mg/cm^2.hr. Similar responses have been recorded from all four animals used in the study.

Figure 26 illustrates the relationship between sweating rate as recorded from the lateral calf as a function of different levels of clamped hypothalamic temperature. This animal had been allowed to equilibrate for one hour at an ambient temperature of 38^{o}C and 20% relative humidity. The rectal and inner thigh skin temperature remained constant during the experiment and averaged 39.1 and 37.7^{o}C respectively. The local skin temperature under the sweat capsule (Tsl) was maintained constant at 35^{o}C throughout the experiment thus eliminating any local skin temperature effects upon the measured sweating activity. Each data point represents the average sweat rate recorded from the lateral calf over a three to five minute period associated with different levels of clamped hypothalamic temperature. All parameters were allowed to return to control levels (five to ten minutes) between subsequent hypothalamic perfusion periods.

A significant linear correlation ($r = 0.97$) was observed between local sweating activity and increasing hypothalamic temperature. The slope of the relationship was 7.44 mg/cm^2.hr.^{o}C. Furthermore, extrapolation of the relationship to the zero sweat rate indicates that the hypothalamic set point for the appearance of sweat on the general body surface under these thermal conditions was 38.06^{o}C.

To investigate the effects of skin temperature upon the sweat rate versus hypothalamic relationship, the experiment was repeated at a lower ambient of 36^{o}C with 20% relative humidity. At this lower ambient the animals rectal temperature equilibrated at 38.9^{o}C and was only 0.2^{o}C lower than in the 38^{o}C environment. The equilibrated skin temperature, however, was significantly lower and averaged 36.4^{o}C. Local skin temperature was maintained constant at 35^{o}C. As illustrated in figure 27 a significant linear correlation ($r = 0.96$) was again obtained between sweat rate on the lateral calf and hypothalamic temperature. The slope of the relationship was 7.97 mg/cm^2.hr.^{o}C and was not significantly different from that shown in figure 26. Extension of the relationship, however, to zero sweat rate indicates that the hypothalamic set point for sweating on the general body surface under these conditions was 38.66 which is significantly higher ($P < .05$) than the set point obtained with the higher skin temperature.

Figure 28 summarizes our findings of the interrelationship between sweat rate, hypothalamic temperature, and skin temperature in the rhesus monkey. We found a significant linear relationship between hypothalamic temperature and sweat rate at two different mean skin temperatures. A decrease in skin temperature produced a significant parallel shift in the relationship to the right resulting in no significant change in the slope but a statistically significant increase in hypothalamic threshold for the appearance of sweat on the general body surface of this animal. Our data support the concept that central body temperature, in this case hypothalamic temperature and skin temperature, interact additively in the control of sweating in Macaca mulatta.

8. A study of the role of hypothalamic temperature in activation or suppression of the sympathico-adrenomedullarysystem in the rhesus monkey. During the grant period we used the micro-flurometric assays for catecholamine developed at the Institute of Environmental Stress in Santa Barbara, California

in conjunction with our hypothalamic water perfusion system in an attempt to quantitate the influence of hypothalamic temperature on the activity of the sympathico-adrenomedullary system. Basically the question we were asking was what is the relationship, if any, between acute step changes in hypothalamic temperature and the circulating levels of epinephrine and norepinephrine which are known to effect metabolic rates and consequently thermoregulation.

The general protocol for these experiments was as follows. Implanted male rhesus monkeys were placed in a familiar restraining chair in a climatic chamber maintained at 25°C. The circulating chamber was secured to the animals' skull acrylic cap for hypothalamic temperature clamping as previously described. The animals saphinous vein was then cannulated and a PE 60 catheter was threaded centrally into the illiac vein. The peripheral end of the catheter and connecting stopcock were taped to the animals' leg. This system permitted repeated blood sampling from the illiac vein without traumatizing the animal. In the majority of the experiments, the monkey was not cognizant of the fact that blood samples were being collected.

Following cannulation of the vein the animals were allowed to sit quietly in the chair for a minimum of one hour at which time two control blood samples were collected. Immediately after the second blood sample was taken the hypothalamic perfusion system was activated and the hypothalamic temperature was clamped at either 0.3°C or 2.0°C above or below neutral temperature. The clamped hypothalamic temperature was maintained constant at one of these altered states for 15 minutes during which time two experimental blood samples were collected. One blood sample was taken within one minute after initiating of the clamping period and another sample was collected on the 15th minute at which time the perfusion period was stopped and the hypothalamic temperature was allowed to return toward control levels and a final blood sample was collected.

Figure 29 demonstrates the mean level of circulating plasma norepinephrine at neutral and as a function of clamped hypothalamic temperature. The number above each bar represents the number of determinations obtained in three different monkeys and the lines illustrate the standard error of the means. It can be seen that the control level of plasma norepinephrine in the rhesus monkey averages 2.45 $\pm$ 21 ng/ml. This value for norepinephrine as well as our control value for epinephrine given below tends to be toward the upper end of the normal range for the human but does not appear to be significantly different from data reported from other species such as the miniture pig. Heating the hypothalamus to 0.3°C above neutral for 15 minutes produced no change in the level of circulating norepinephrine while cooling the hypothalamus to the same degree produced a slight (2.45 to 2.57) but insignificant rise in plasma norepinephrine. It can also be seen from figure 12 that heating the hypothalamus to 2.0°C above neutral for 15 minutes results in no change in the level of circulating plasma norepinephrine. Cooling the hypothalamus to 2.0°C below neutral, on the other hand, causes a 15% rise in norepinhephrine from the control value of 2.45 to 2.82 ng/ml. The rise, however, was not statistically significant at the .01 level.

Figure 30 illustrates the relationship between plasma epinephrine and hypothalamic temperature of the rhesus monkey. It can be seen that the level of circulating plasma epinephrine in our group of animals averaged 1.52 ± .20 ng/ml. We found that neither heating nor cooling of the hypothalamic area for 15 minutes to 0.3°C above or below neutral temperature had any significant effect upon the circulating levels of epinephrine. Heating the hypothalamus to 2.0°C above neutral produced a 12% drop in mean plasma epinephrine from 1.52 ng/ml. The change however was not statistically significant. Cooling of the hypothalamus, on the other hand, resulted in a 34% increase in plasma epinephrine from its control value of 1.52 ng/ml to 2.03 ng/ml. This increase in epinephrine, although not significant at the .01 level was significant at the .05 level.

We conclude from these studies, therefore, that short term changes in temperature of the order of 0.3°C above or below neutral hypothalamic temperature do not play a significant role in activation or suppression of the sympathico-adrenomedullary system of the rhesus monkey. Although clamping of the hypothalamic temperature at 2.0°C above neutral tended to suppress the sympathico-adrenomedullary system resulting in decreases in the circulating levels of plasma catecholamines while clamping hypothalamic temperature for 15 minutes at 2.0°C below neutral tended to increase the output of the sympathico-adrenomedullary system as indicated by an increase in the level of circulating catecholamines, the changes observed were not statistically significant at the .01 level. We found no significant coupling between hypothalamic temperature and plasma catecholamines in rhesus monkeys equilibrated to an ambient temperature of 25°C.

9. Studies of the cardiovascular and body fluid compartments in non-heat stressed rhesus monkeys. In the last year of the grant we used the excellent isotope facilities at the Institute of Environmental Stress to initiate a study designed to provide base line normal values for the cardiovascular and body fluid compartments in the rhesus monkey. Some of the results of these studies are summarized in Table IV . The first column lists some of the parameters that were measured using standard isotope dilution techniques as well as those that could be calculated from the measured data. The second column gives the value for each parameter plus or minus the standard error of the mean and finally the number of determinations done on a total of four different animals.

Table IV: Cardiovascular and Body Fluid Compartments in the Rhesus Monkey

PARAMETER	VALUE ± S.E.	DETERMINATIONS
Body Weight	6.16 ± .36 Kg	27 (4)
Red Cell Vol.	19.1 ± 2.2 ml/Kg	20
HCT. X 0.91	35.8 ± 1.3 %	32
Plasma Prot.	7.15 ± 0.35 gm %	30
Total Body H_2O	694 ± 11.0 mg/Kg	10
Extracellular H_2O	264 ± 8.2 ml/Kg	19
Intracellular H_2O	430 mg/Kg	
Blood Vol.	53 ml/Kg	
Plasma Vol.	34.2 ml/Kg	

Rhesus monkey red cells were tagged with chromium 51 and used to measure circulating red cell volume which in our group of four make monkeys averaged 19 ml/kg. The venous hematocrit corrected for an F cell ratio of .91 was 35.8% while total plasma protein averaged 7 mg%. Tritium labeled water was used to measure total body water which averaged 694 ml/Kg. Sulfur 35 was used to estimate the extracellular compartment and averaged 264 ml/Kg. Intracellular water could then be calculated and in this group of animals averaged 430 mg/Kg.

Since circulating red cell volume and hematocrit were directly measured we could then calculate that the total blood volume of the rhesus monkey was equal to 53 ml/Kg, furthermore, by subtracting the red cell volume from the total blood volume we could estimate tht total plasma volume of the animals at 34 ml/Kg.

It is interesting to note that although the total blood volume of the rhesus monkey appears somewhat lower than the value of 70-75 ml/Kg commonly reported for man, the ratio of plasma to red cells is the same giving an uncorrected hematocrit of approximately 40%. Furthermore, the total body water, the extracellular water compartment, and the intracellular water compartment, when examined on a unit body weight basis appears to be quantitatively similar to those reported for the human. In the future, therefore, we plan to extend these studies to cold and heat acclimated monkeys to determine the magnitude and the role that body fluid shifts might play in the ability of higher primates to adapt to various types of thermal stress.

10. Control of palmar sweating in man. The observation that sweating from the palms of the hand of the rhesus monkey was synchronized with sweating from the general body surface (Figure 2) suggested, for the first time that palmar sweat glands would respond to thermoregulatory stimuli. Previous studies had suggested that palmar sweat glands of man only respond to emotive stimuli, and this phenomenon has been used as the basis for the galvanic skin resistance (GSR) test in psychological studies. It was important to know therefore, if stimuli other than those of emotive origin, would influence these glands. For the accurate measurement of water loss from small areas of skin a new type of humidity sensor was utilized. This consisted of a Brady Array (Thunder-Scientific, Albuquerque, New Mexico) which has a very fast response time coupled with high sensitivity. Air of controlled and known humidity has drawn through a capsule sealed on to the skin and then passed over the humidity sensor whose output was amplified, displayed on an oscilloscope and recorded both on tape and on a potentiometric chart recorder. The system was calibrated with a humidity generator (Panametrics, Waltham, Massachusetts). Sweat rate measurements from the palms, soles of feet and forearm were made concurrently. Insensible water loss, i.e. the simple diffusion of water across the epidermal barrier and was found to be 36 $gm/m^2/hr$. for the palms and 19 $gm/m^2/hr$ for the forearm. Insensible water loss from the forearm is typical of that from the general body surface but the high loss from the palms is unusual. The epidermal barrier to water loss is generally considered to reside in the stratum carneum of the skin but histological examination of skin from the palms and forearm revealed no obvious difference in the stratum corneum between the two sites. The explanation for the high rate of water diffusion of palmar and solar skin remains unexplained.

Three distinct stimuli were found to activate palmar sweating, and the responses from both palms and soles of the feet were synchronous. The stimuli were: 1) Heat exposure. Sweating from the palms and soles was synchronous, in the resting subject with that from the forearm in a manner similar to that described for the rhesus monkey. 2) Emotive stimulation. Stimuli such as mental arithmetic and memorization of w rds proved potent stimuli of both palmar and solar sweating. This was superimposed on heat-induced sweating. 3) Exercise. Sweating from the palms and soles started within 5 seconds of the start of exercise and was related to degree of limb movement rather than the severity of exercise, e.g. on a bicycle ergometer sweat rate from the palms was related to frequency of pedalling and not the work load. At work loads in excess of 60% of $\dot{V}_{O2}$ max sweat rate declined. Passive exercise had no stimulatory effect on palmar sweating. The response to exercise was superimposed on that induced by heat exposure.

It was concluded from this study that palmar and solar sweat glands have a dual innervation. The hypothesis that was developed for palmar sweat gland control, was that the glands are controlled in a manner similar to those on the general body surface, i.e. they possess a thermoregulatory function. They have an additional nerve supply which probably innervates the myoepithelial cells and responds to emotive and exercise, i.e. limb movement stimuli. It was not possible to separate these two stimuli which may therefore have a common efferent pathway. The decline in palmar sweating at high work loads was probably due to epinephrine secretion which had previously been shown to cause palmar anhidrosis.

Figure 1

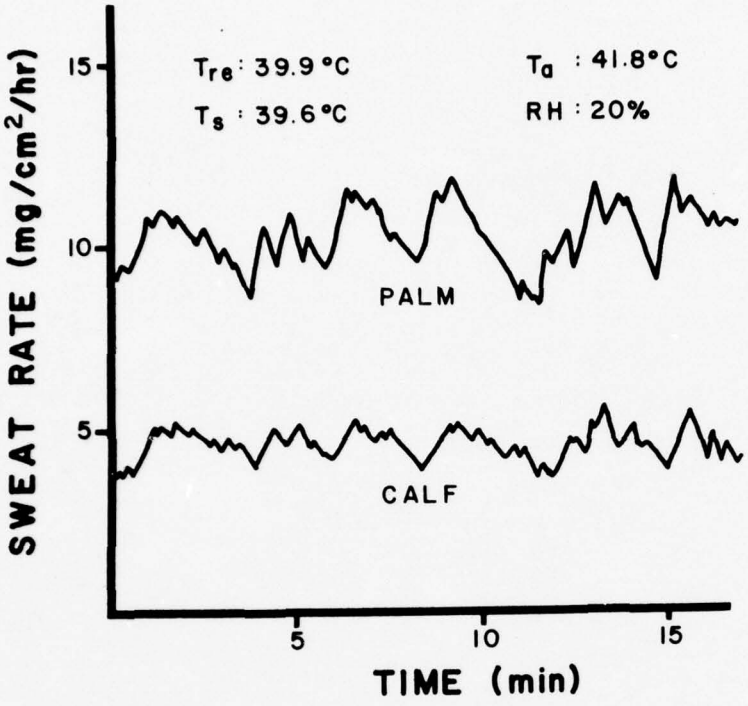
SWEAT RATE (mg/cm²/hr)
15
10
5
T_{re} : 39.9 °C
T_s : 39.6 °C
T_a : 41.8°C
RH : 20%
PALM
CALF
5
10
15
TIME (min)

Figure 2

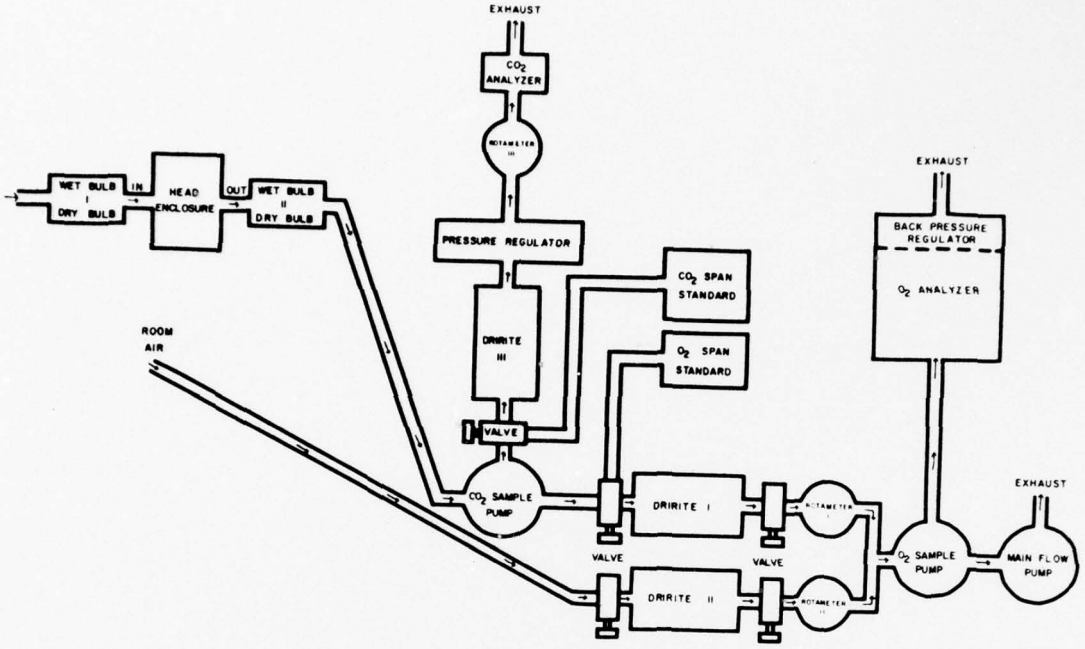

Figure 3

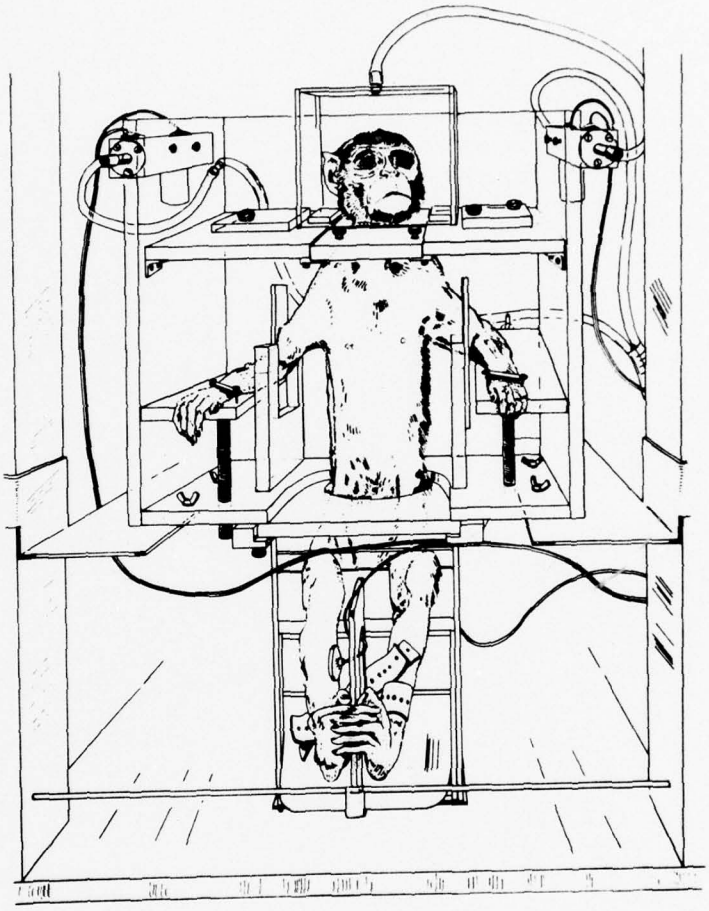

Figure 4

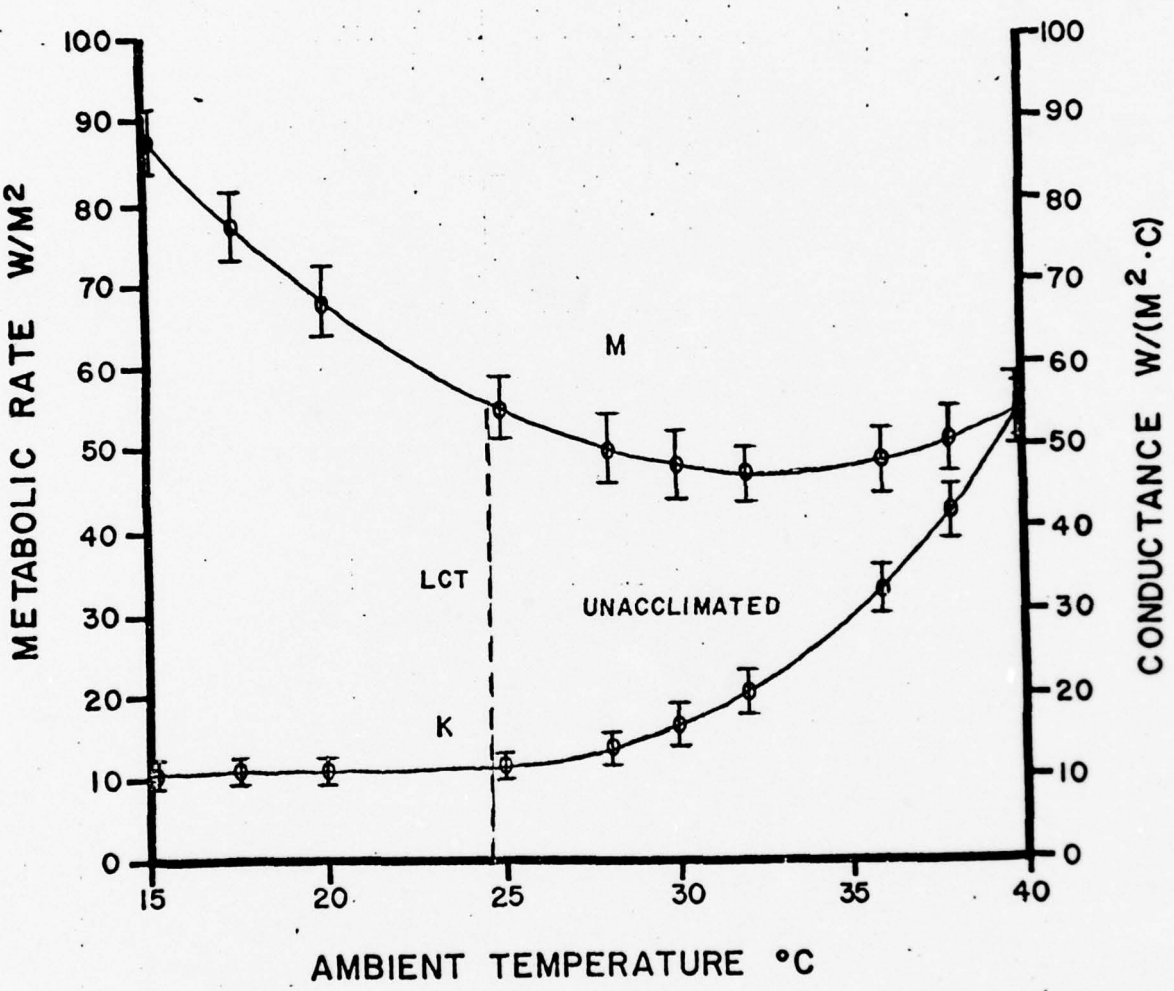
METABOLIC RATE W/M2
CONDUCTANCE W/(M2·C)
AMBIENT TEMPERATURE °C
M
K
LCT
UNACCLIMATED
0
10
20
30
40
50
60
70
80
90
100
15
20
25
30
35
40

Figure 5

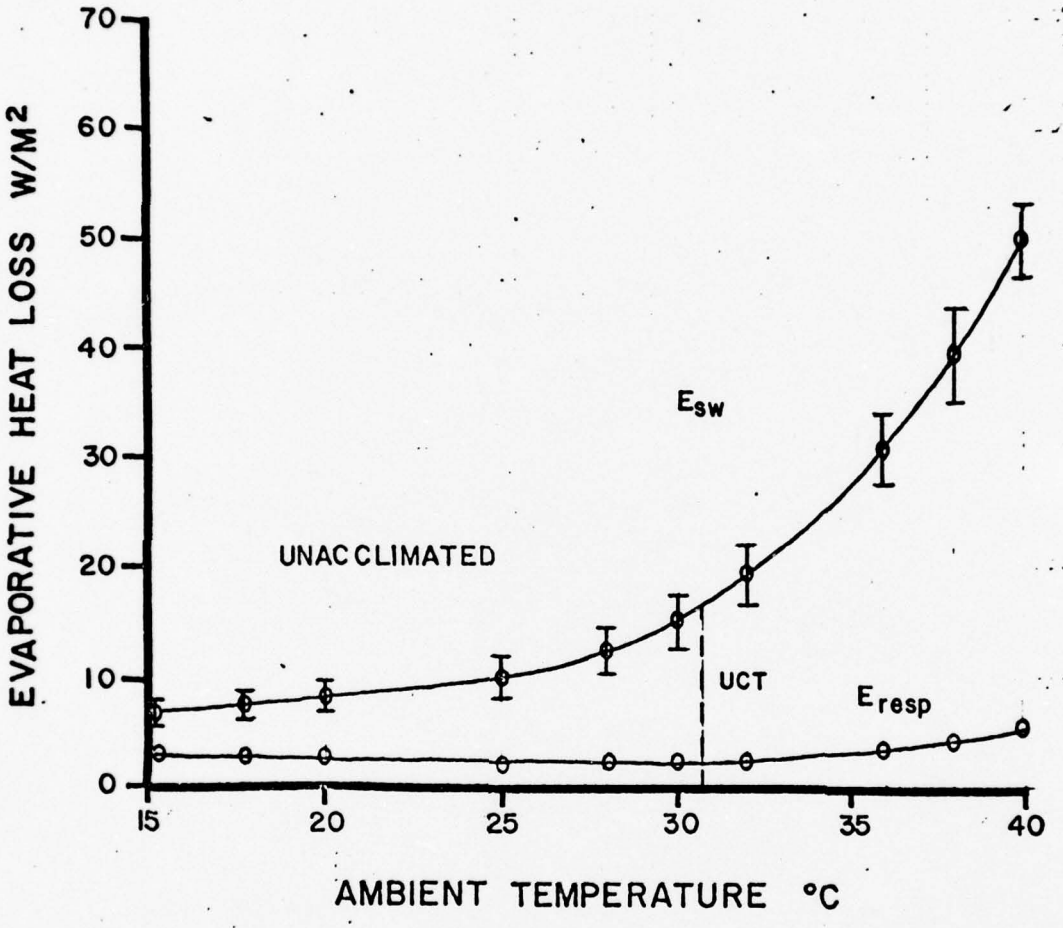
EVAPORATIVE HEAT LOSS W/M2
70
60
50
40
30
20
10
0
15
20
25
30
35
40
AMBIENT TEMPERATURE °C
Esw
UNACCLIMATED
UCT
Eresp

Figure 6

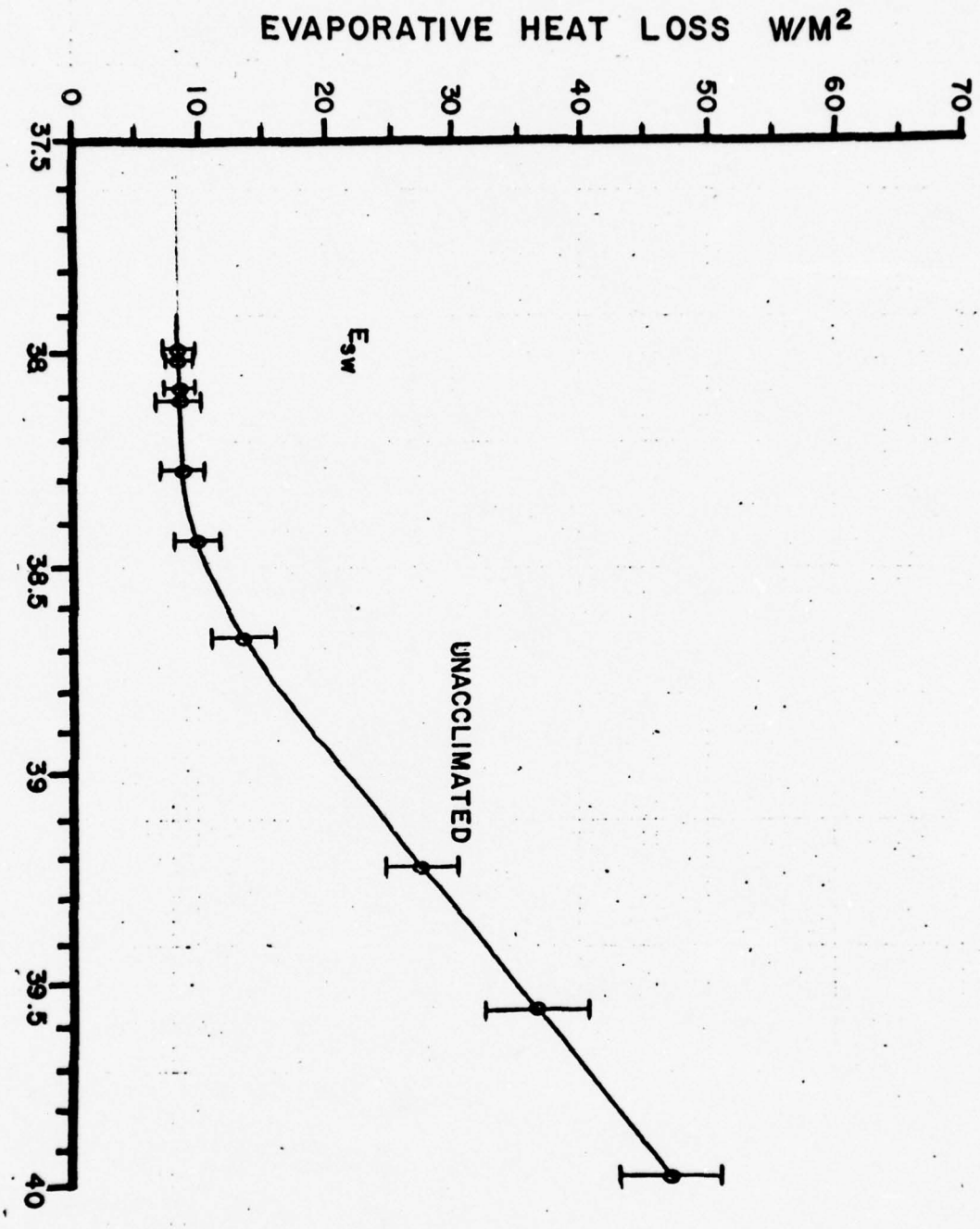
EVAPORATIVE HEAT LOSS W/M²
0
10
20
30
40
50
60
70
37.5
38
38.5
39
39.5
40
RECTAL TEMPERATURE °C
E_{sw}
UNACCLIMATED

Figure 7

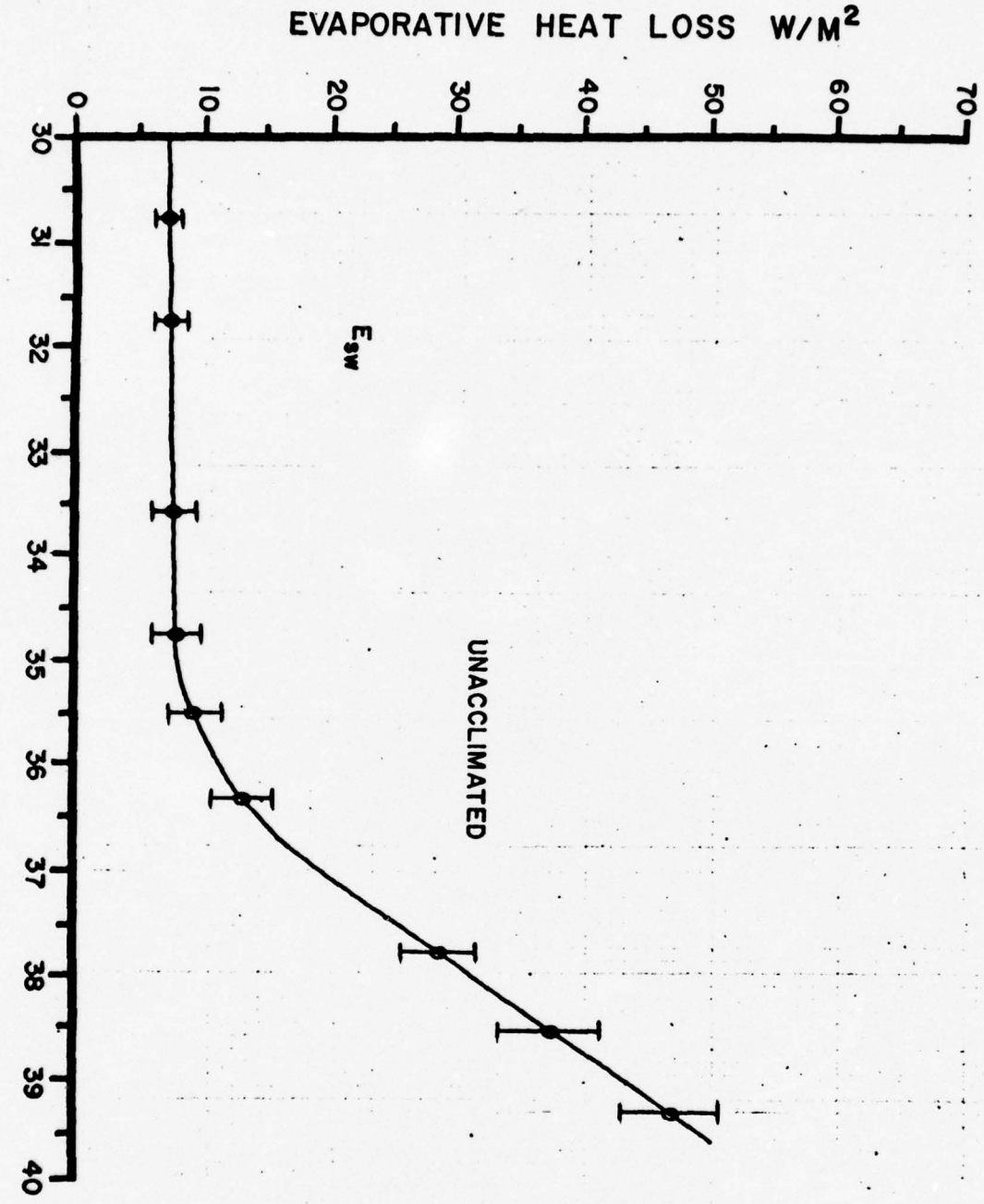
EVAPORATIVE HEAT LOSS W/M²
0
10
20
30
40
50
60
70
30
31
32
33
34
35
36
37
38
39
40
MEAN SKIN TEMPERATURE °C
E_sw
UNACCLIMATED

Figure 8

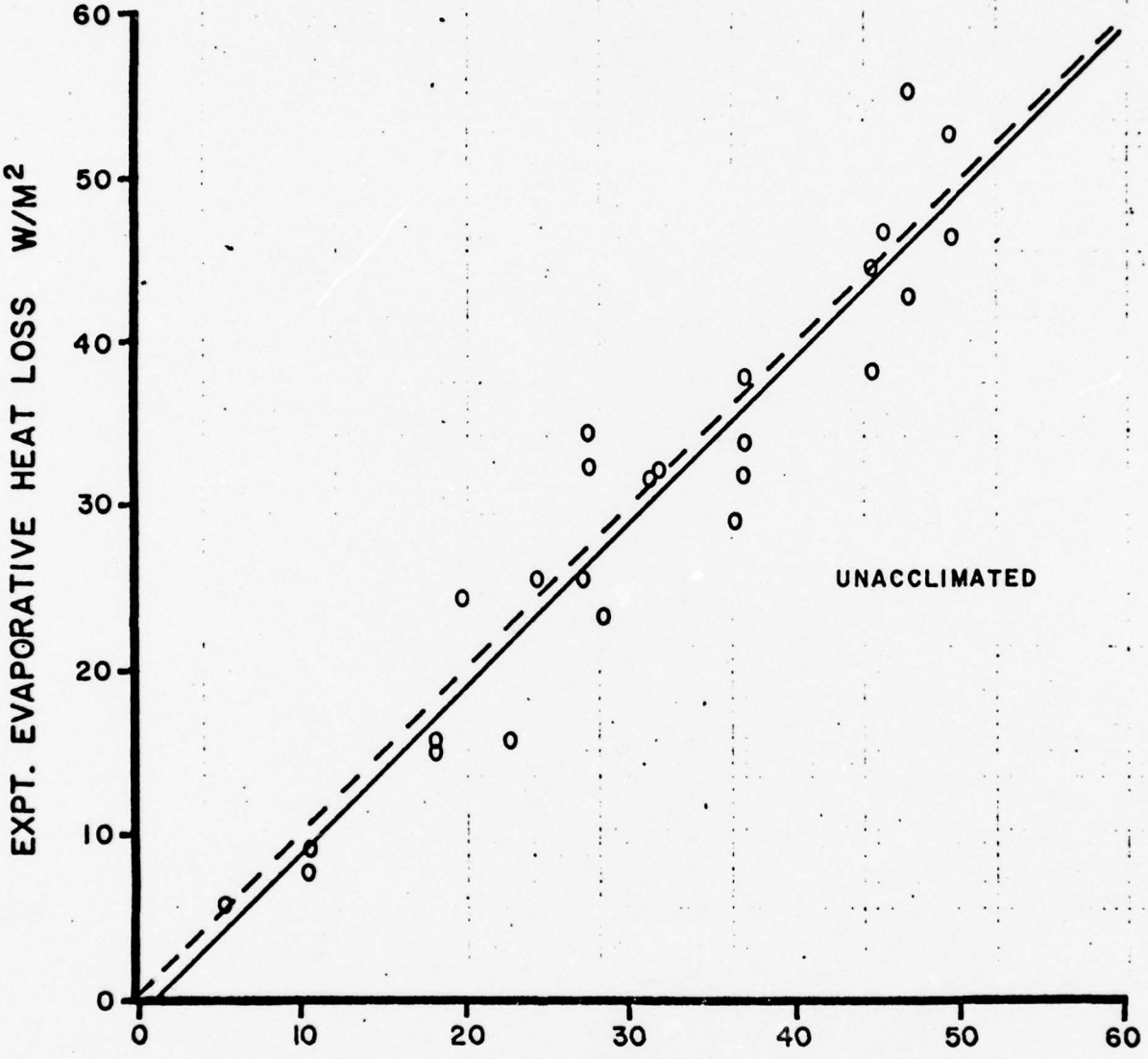
EXPT. EVAPORATIVE HEAT LOSS W/M2
60
50
40
30
20
10
0
0
10
20
30
40
50
60
UNACCLIMATED
$E_{sw} = 9.01(T_{re} - 38.17) + 5.26(T_{\bar{s}} - 35.17)$ W/M^2

Figure 9

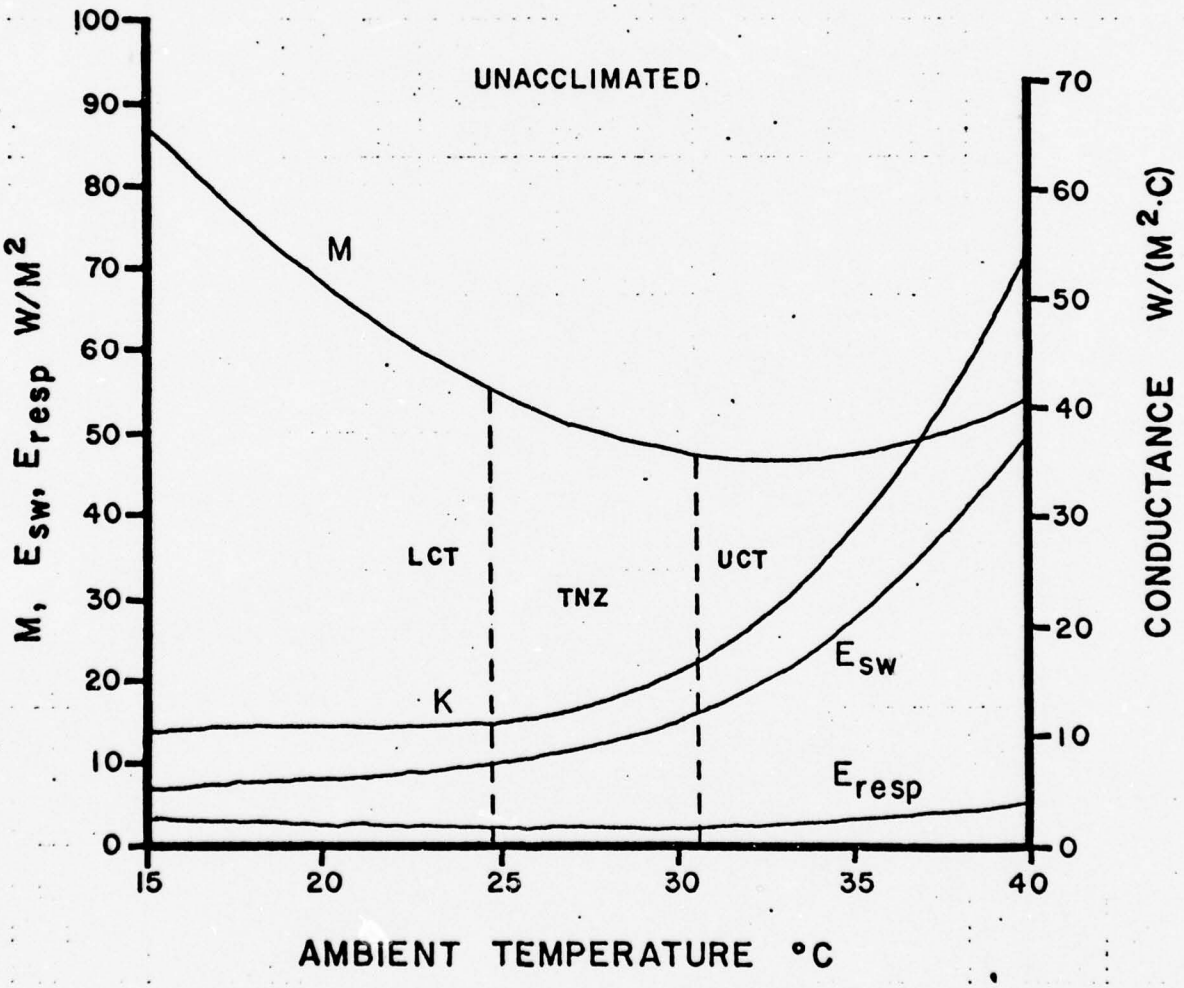
UNACCLIMATED
M
K
E_{sw}
E_{resp}
LCT
TNZ
UCT
M, E_{sw}, E_{resp} W/M^2
CONDUCTANCE W/(M^2·C)
AMBIENT TEMPERATURE °C
100
90
80
70
60
50
40
30
20
10
0
70
60
50
40
30
20
10
0
15
20
25
30
35
40

Figure 10

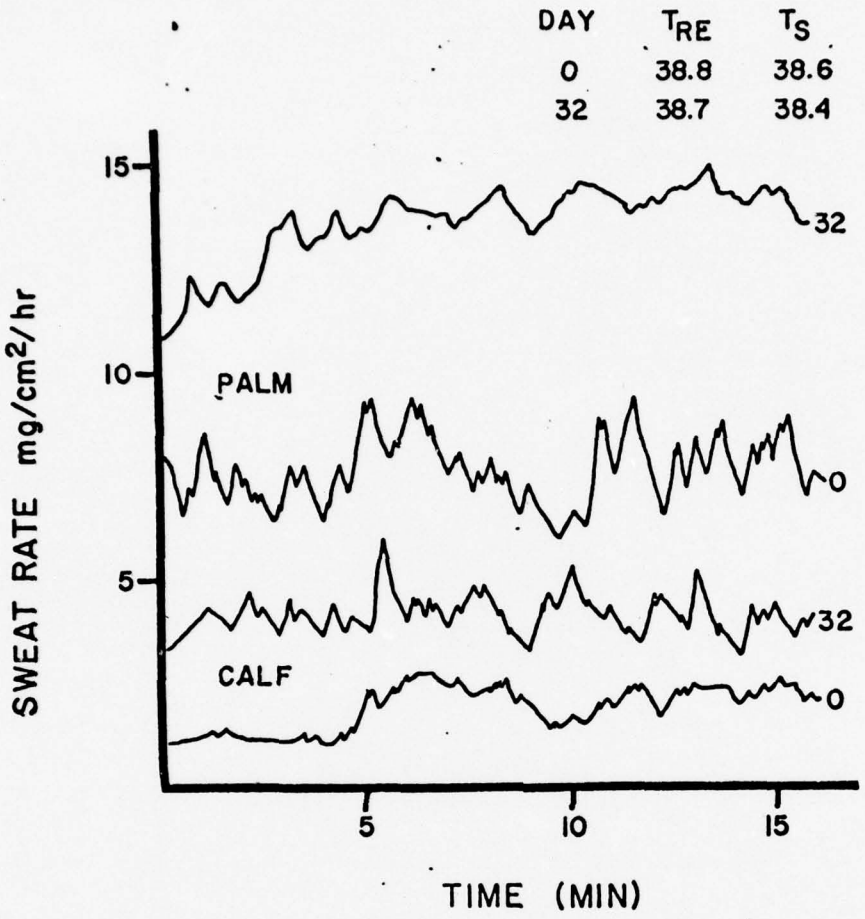
DAY
T_{RE}
T_S
0
38.8
38.6
32
38.7
38.4
15
10
5
SWEAT RATE mg/cm²/hr
PALM
CALF
32
0
32
0
5
10
15
TIME (MIN)

Figure 11

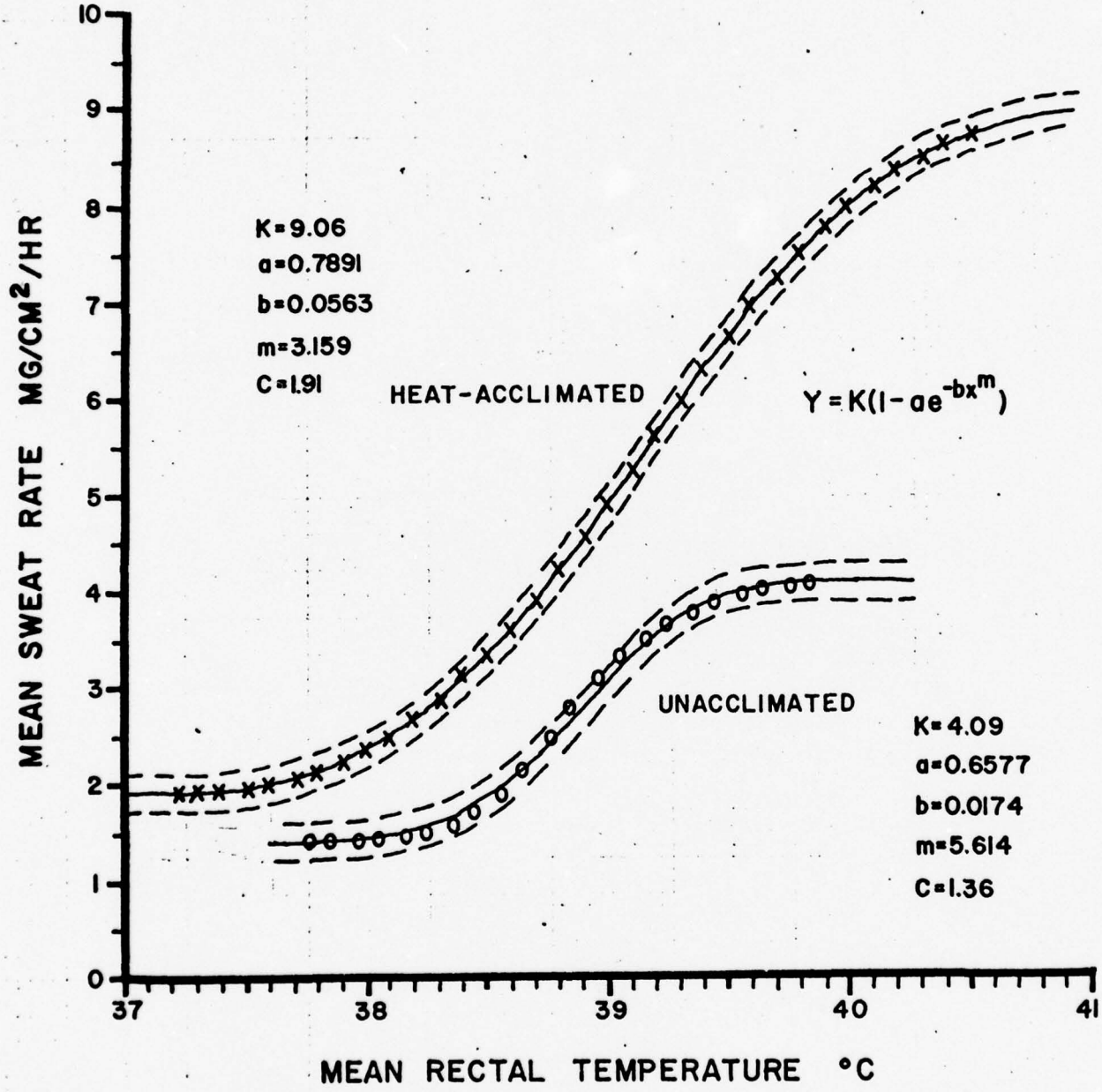
MEAN SWEAT RATE MG/CM²/HR
MEAN RECTAL TEMPERATURE °C
K=9.06
a=0.7891
b=0.0563
m=3.159
C=1.91
HEAT-ACCLIMATED
Y = K(1 - ae^-bx^m)
UNACCLIMATED
K=4.09
a=0.6577
b=0.0174
m=5.614
C=1.36
0
1
2
3
4
5
6
7
8
9
10
37
38
39
40
41

Figure 12

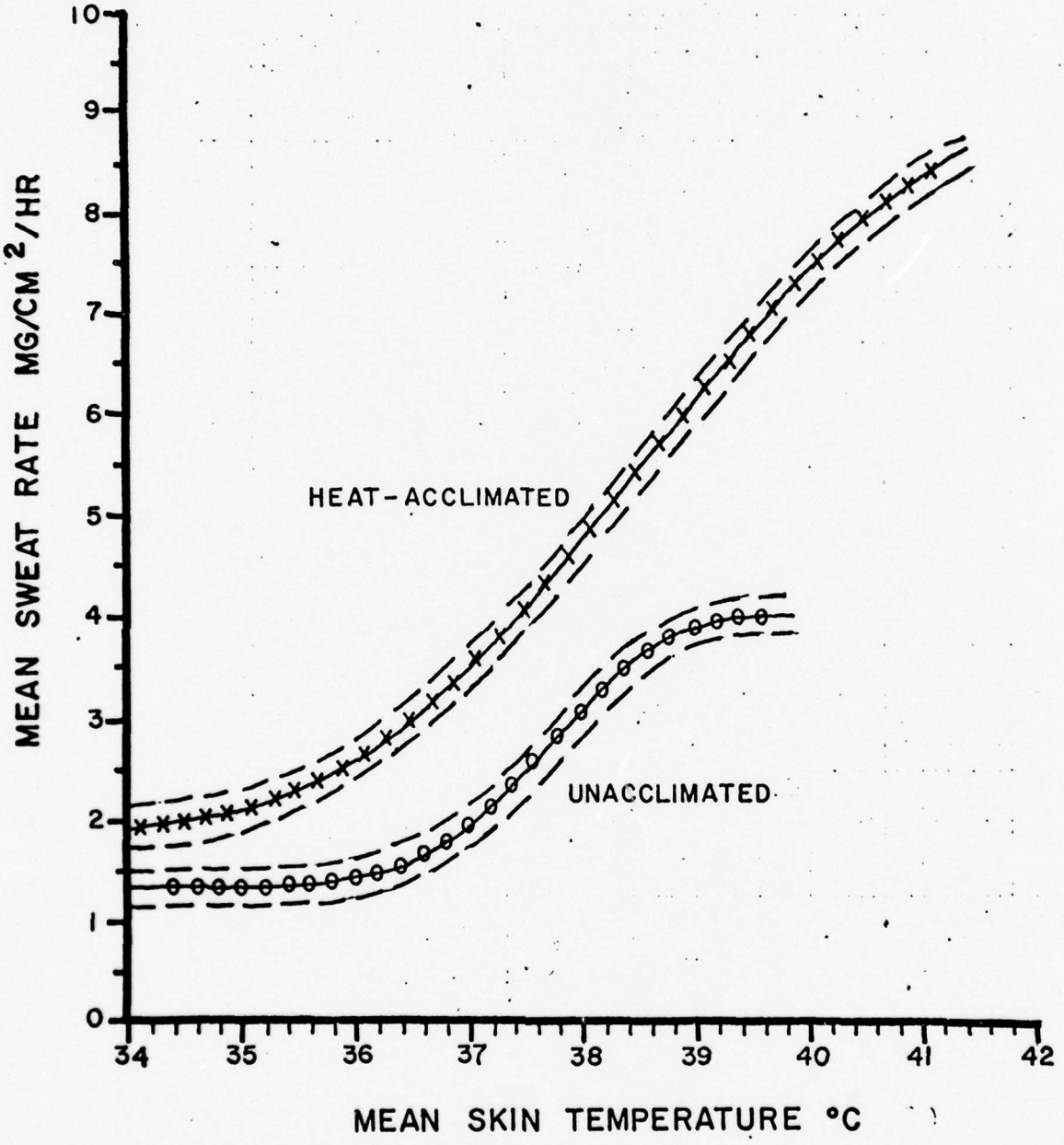
MEAN SWEAT RATE MG/CM 2/HR
10
9
8
7
6
5
4
3
2
1
0
HEAT-ACCLIMATED
UNACCLIMATED
34
35
36
37
38
39
40
41
42
MEAN SKIN TEMPERATURE °C

Figure 13

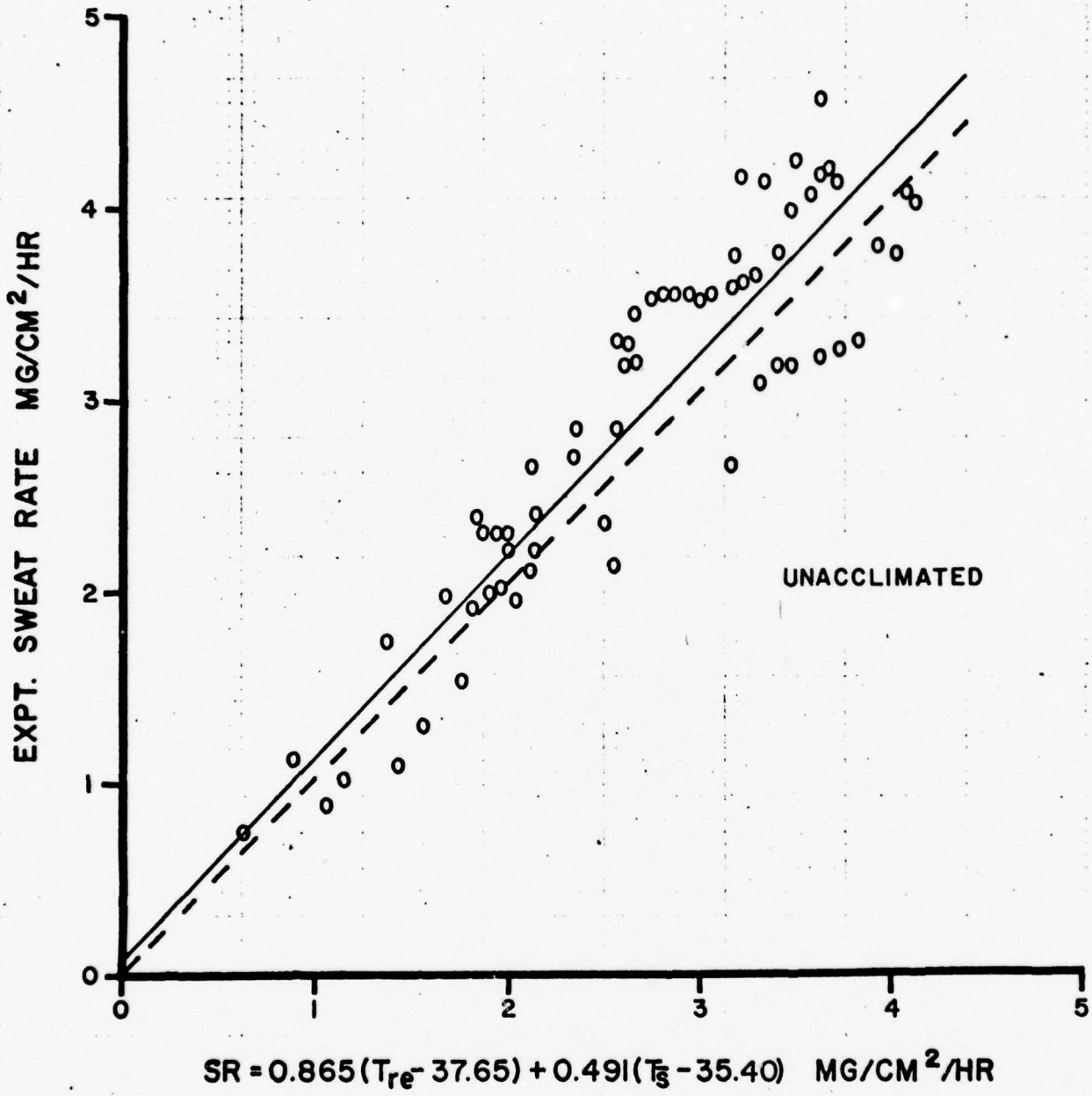
EXPT. SWEAT RATE MG/CM²/HR
0
1
2
3
4
5
UNACCLIMATED
SR = 0.865 (Tre - 37.65) + 0.491 (Tsk - 35.40) MG/CM²/HR

Figure 14

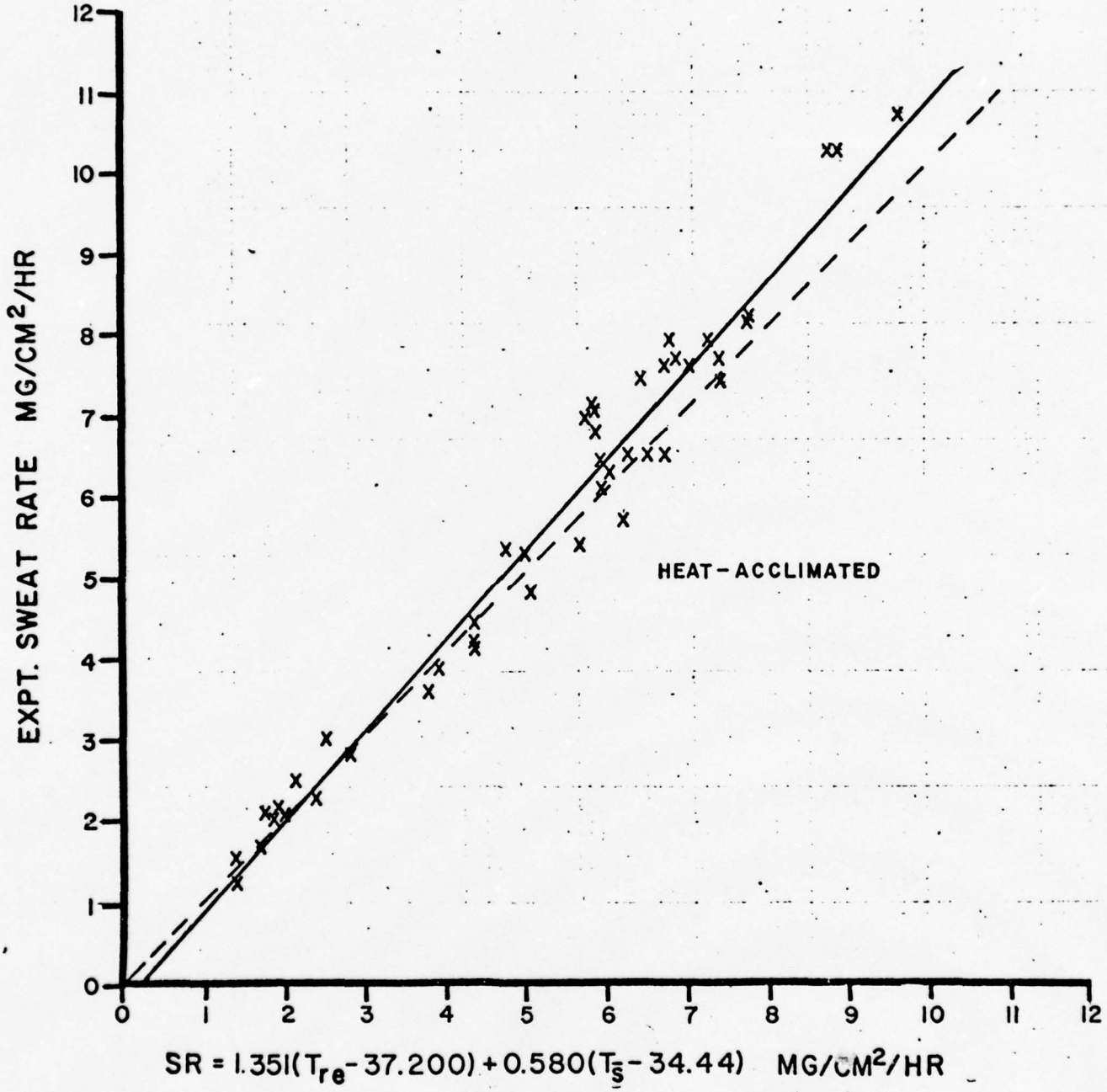
EXPT. SWEAT RATE MG/CM²/HR
HEAT-ACCLIMATED
SR = 1.351(T_re - 37.200) + 0.580(T_s - 34.44) MG/CM²/HR

Figure 15

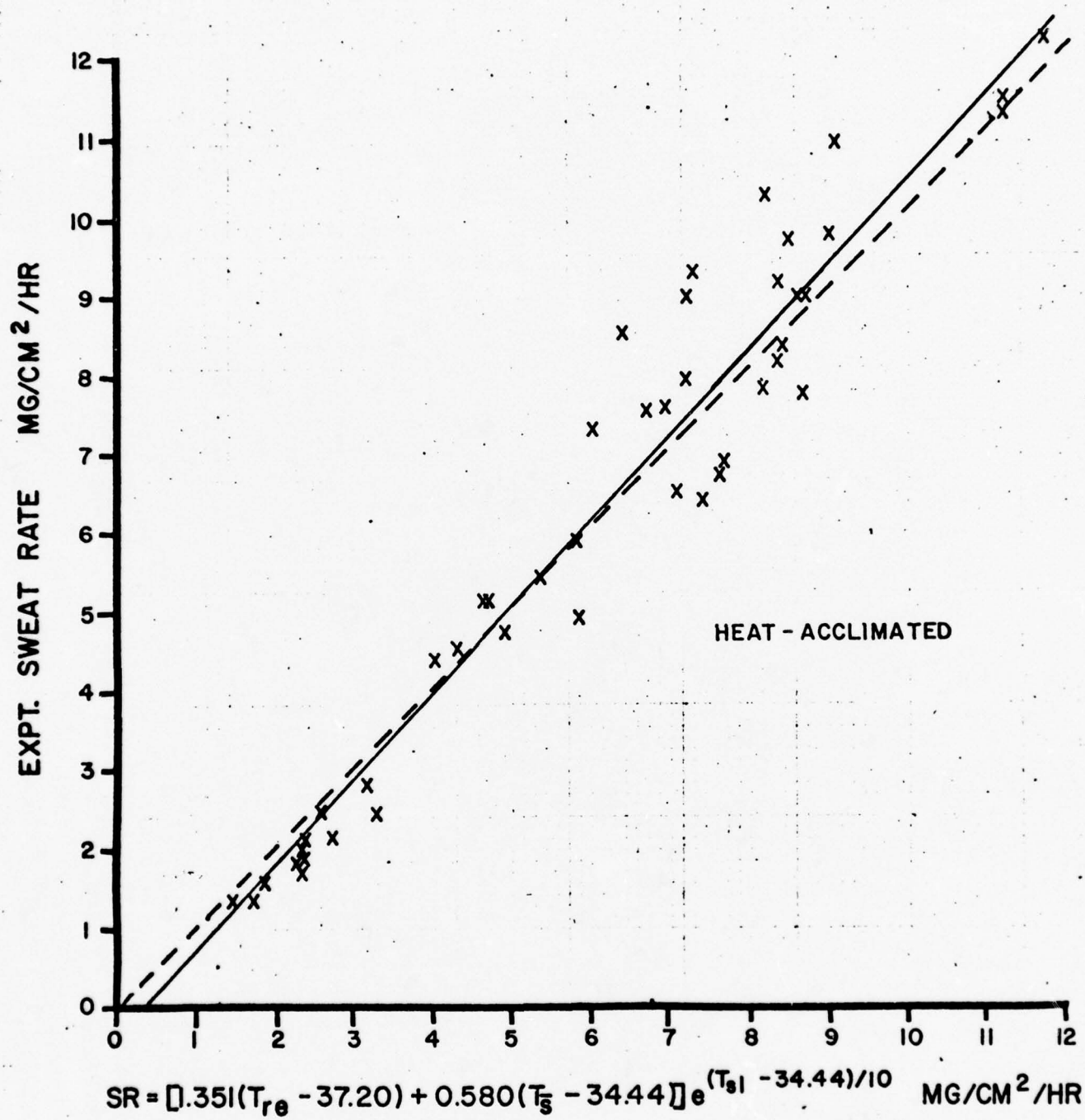
EXPT. SWEAT RATE MG/CM²/HR
HEAT - ACCLIMATED
SR = [].351(T_re - 37.20) + 0.580(T_s - 34.44]] e^(T_sl - 34.44)/10 MG/CM²/HR

Figure 16

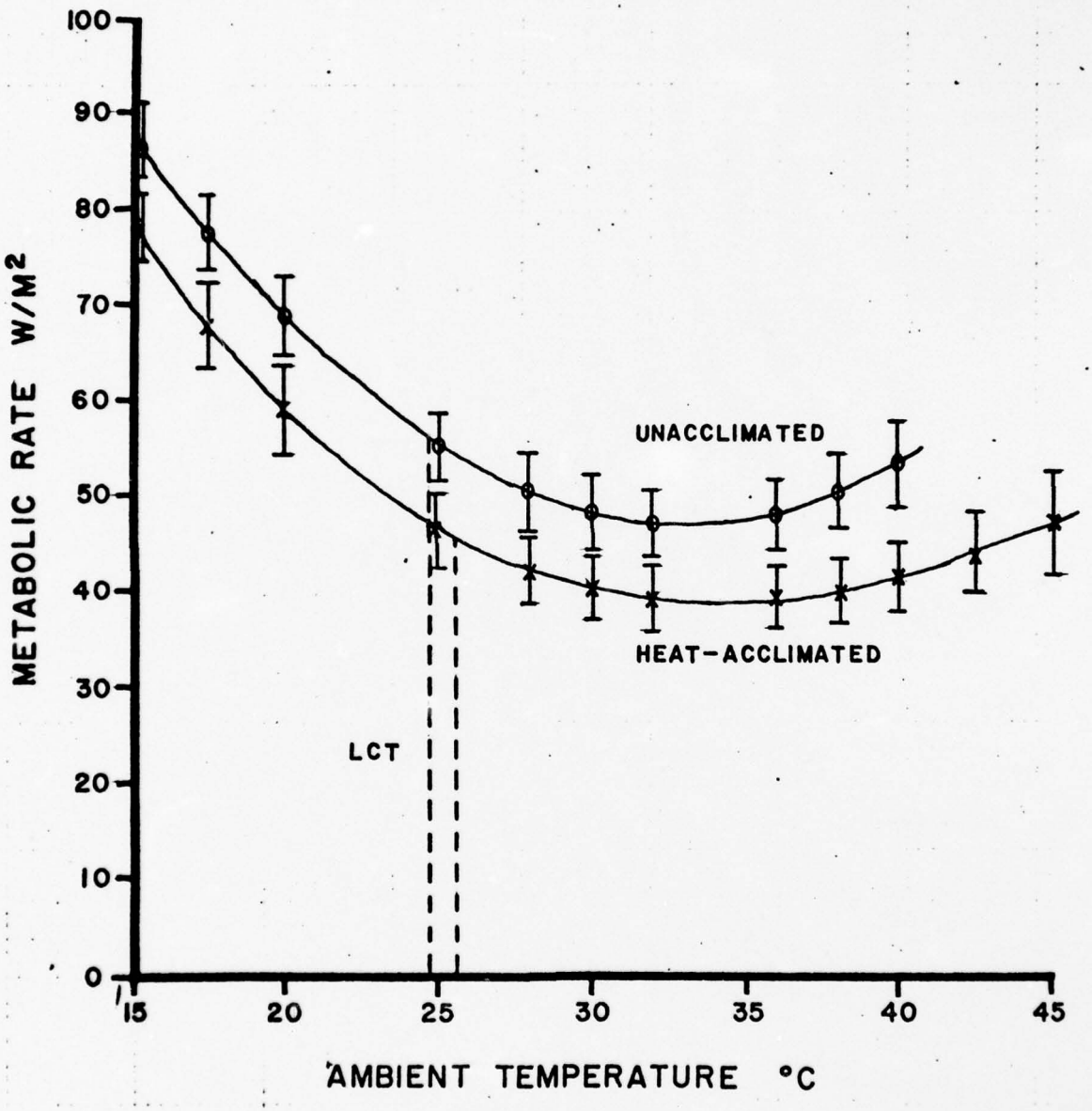
METABOLIC RATE W/M²
100
90
80
70
60
50
40
30
20
10
0
UNACCLIMATED
HEAT-ACCLIMATED
LCT
15
20
25
30
35
40
45
AMBIENT TEMPERATURE °C

Figure 17

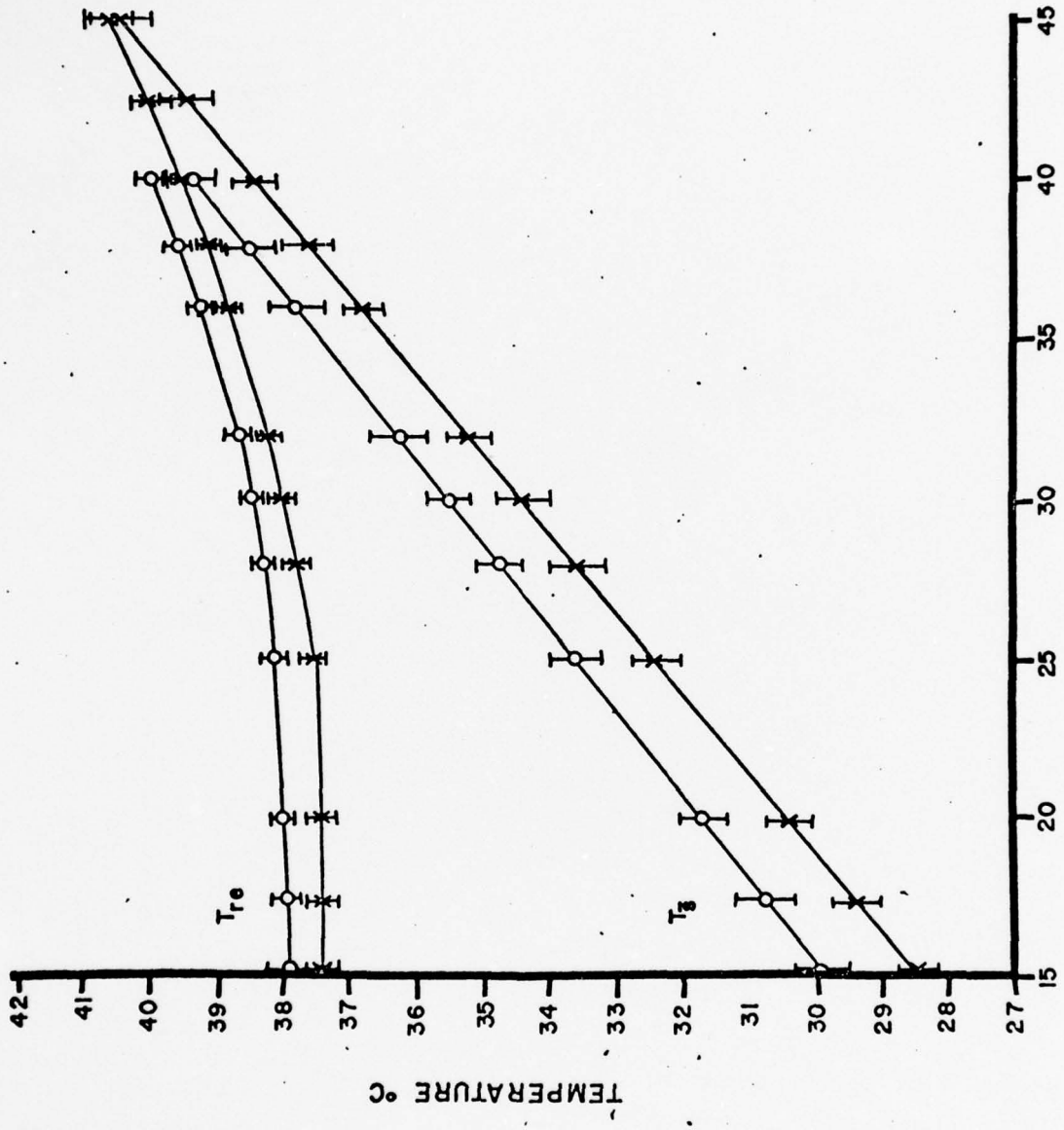
TEMPERATURE °C
AMBIENT TEMPERATURE °C
T_{re}
T_s
42
41
40
39
38
37
36
35
34
33
32
31
30
29
28
27
15
20
25
30
35
40
45

Figure 18

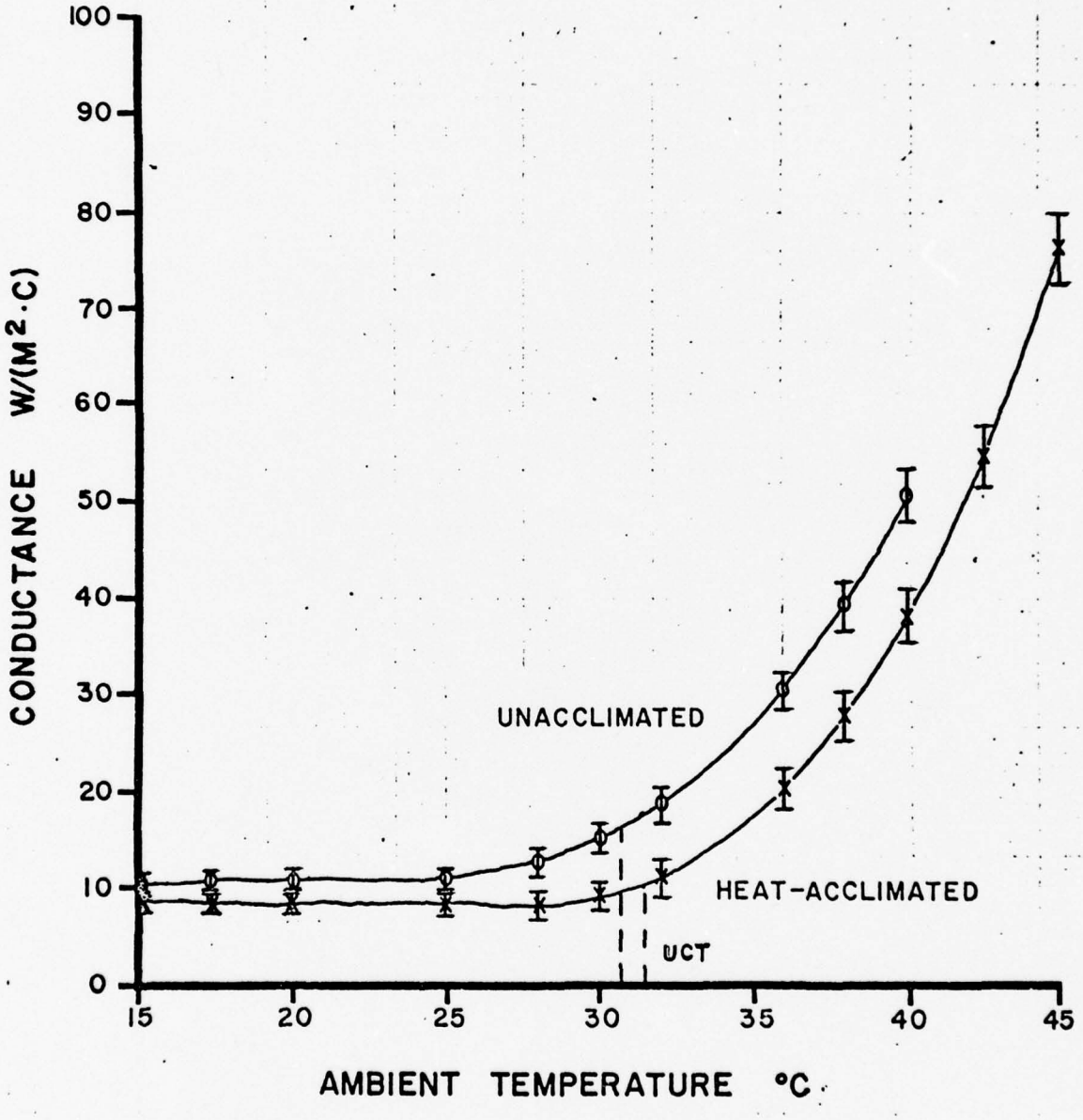
CONDUCTANCE W/(M2·C)
100
90
80
70
60
50
40
30
20
10
0
15
20
25
30
35
40
45
AMBIENT TEMPERATURE °C
UNACCLIMATED
HEAT-ACCLIMATED
UCT

Figure 19

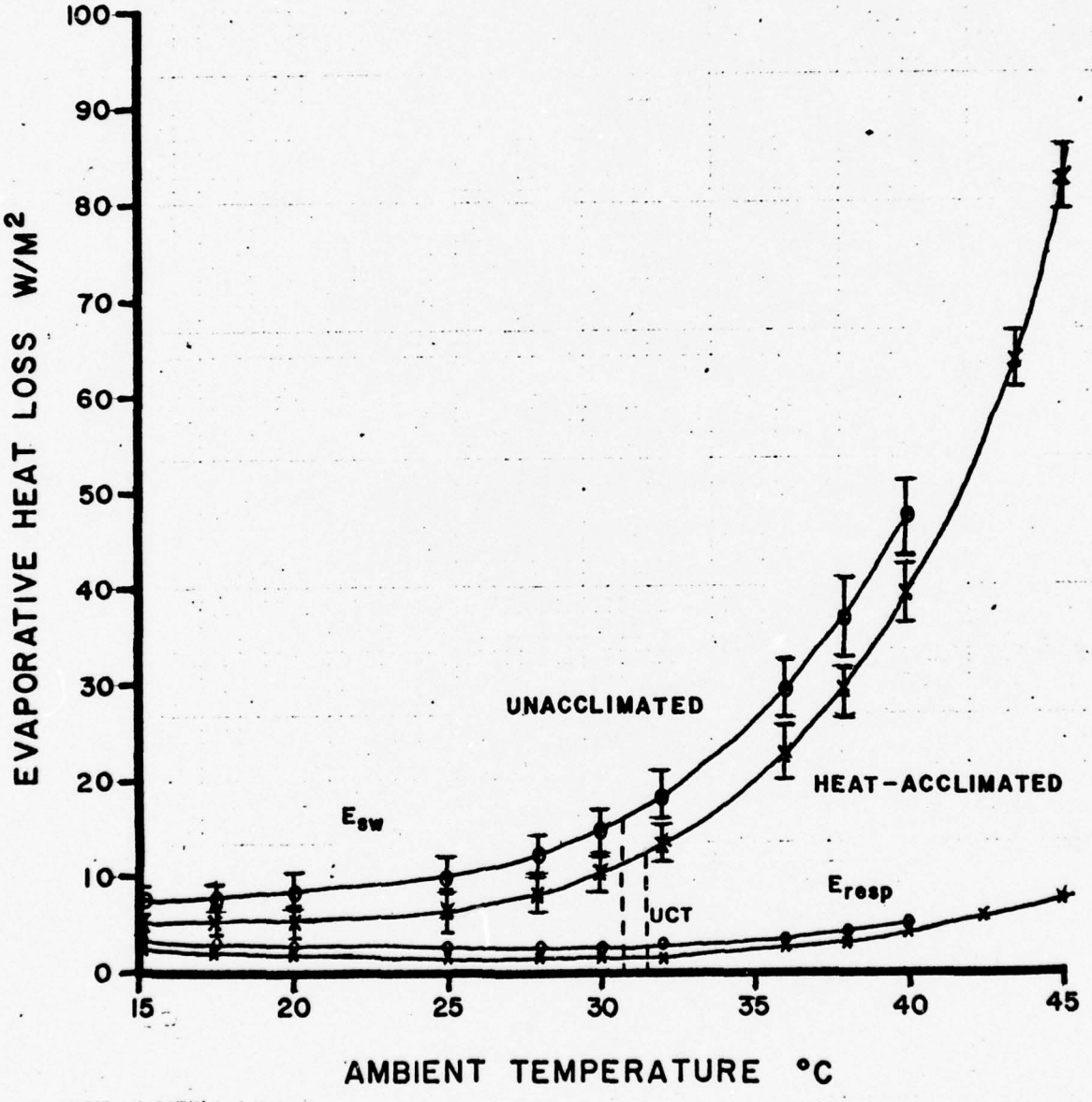
EVAPORATIVE HEAT LOSS W/M²
100
90
80
70
60
50
40
30
20
10
0
15
20
25
30
35
40
45
AMBIENT TEMPERATURE °C
UNACCLIMATED
HEAT-ACCLIMATED
Esw
Eresp
UCT

Figure 20

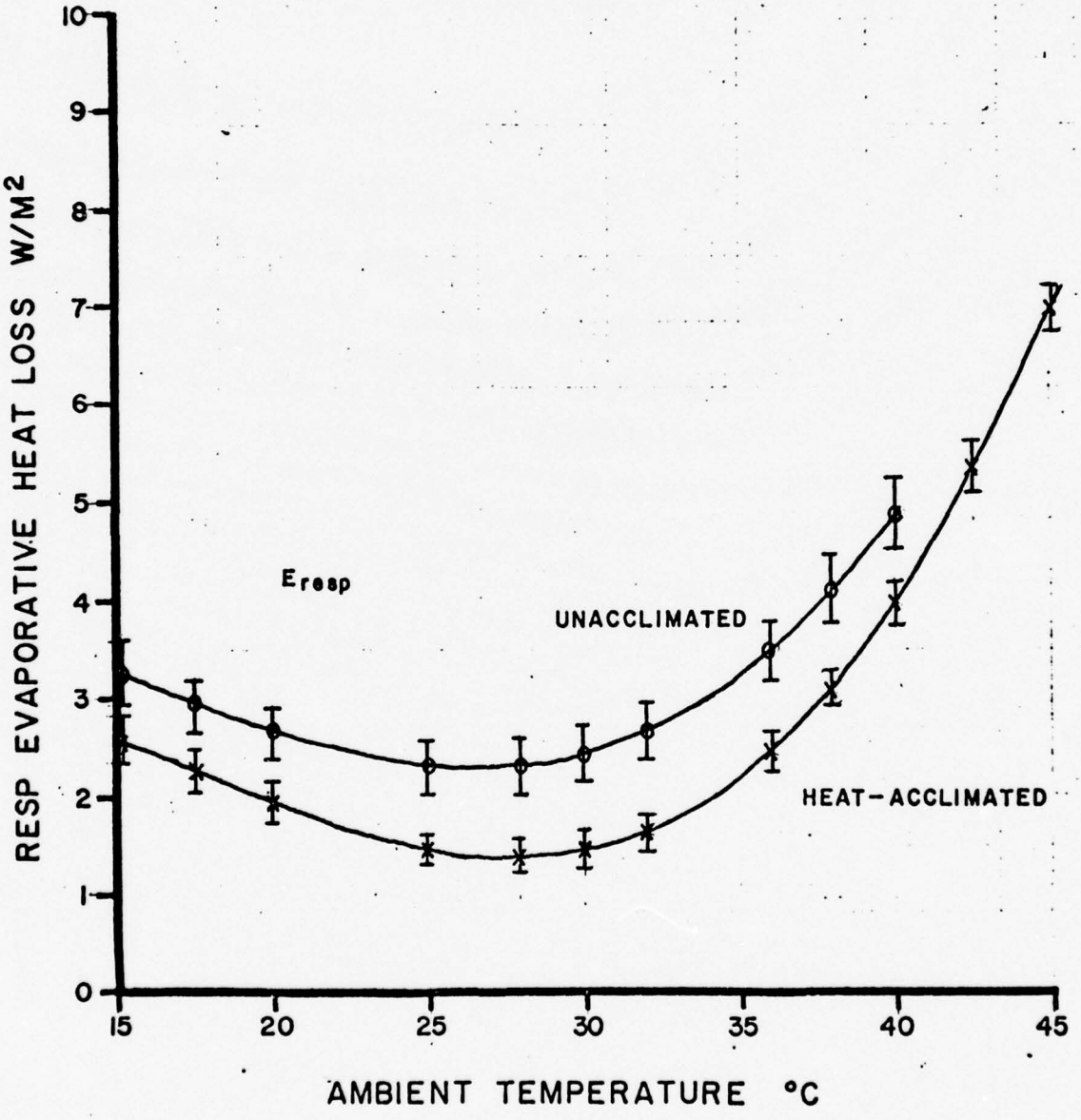
RESP EVAPORATIVE HEAT LOSS W/M²
10
9
8
7
6
5
4
3
2
1
0
Eresp
UNACCLIMATED
HEAT-ACCLIMATED
15
20
25
30
35
40
45
AMBIENT TEMPERATURE °C

Figure 21

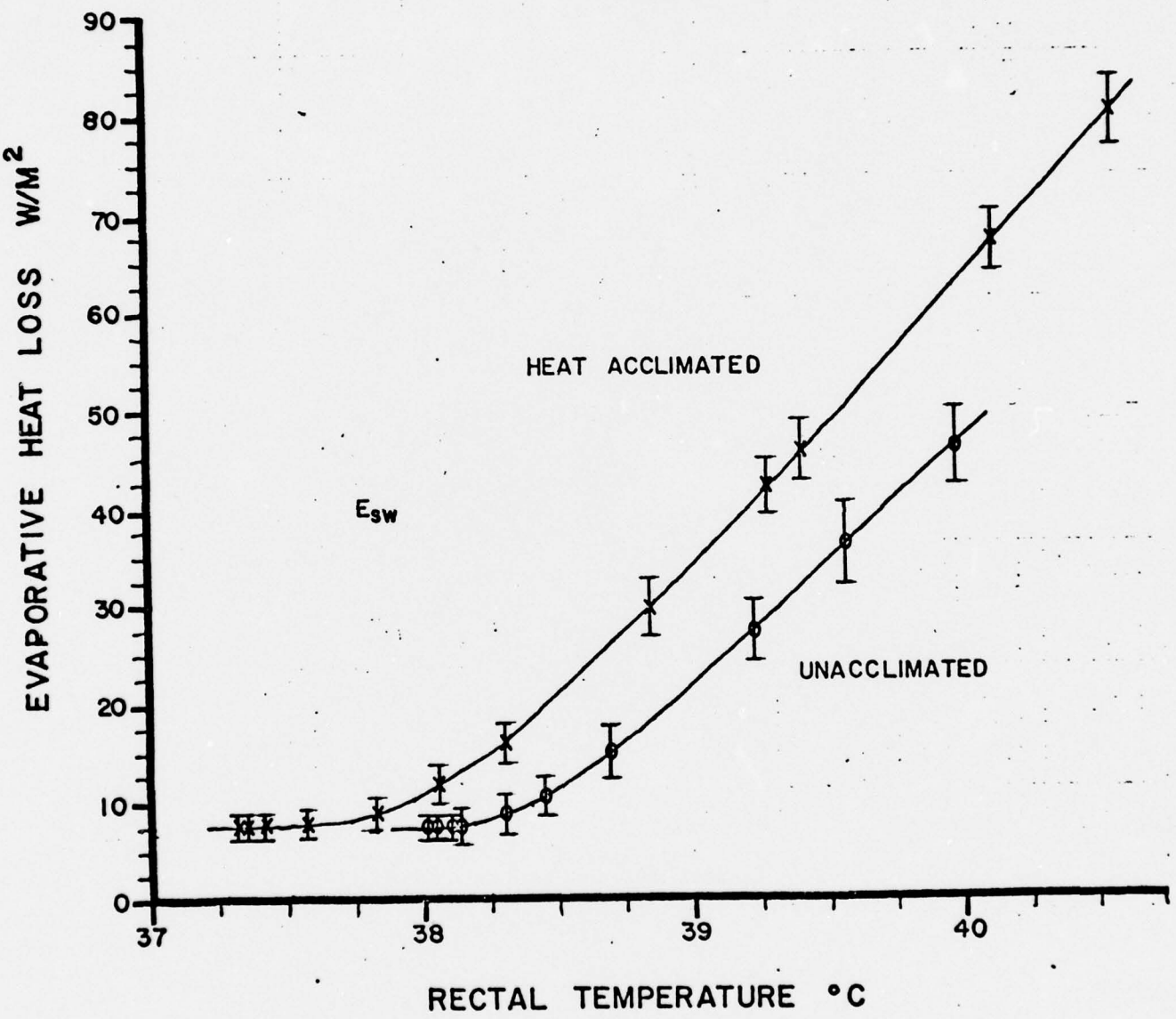
EVAPORATIVE HEAT LOSS W/M²
90
80
70
60
50
40
30
20
10
0
HEAT ACCLIMATED
Esw
UNACCLIMATED
37
38
39
40
RECTAL TEMPERATURE °C

Figure 22

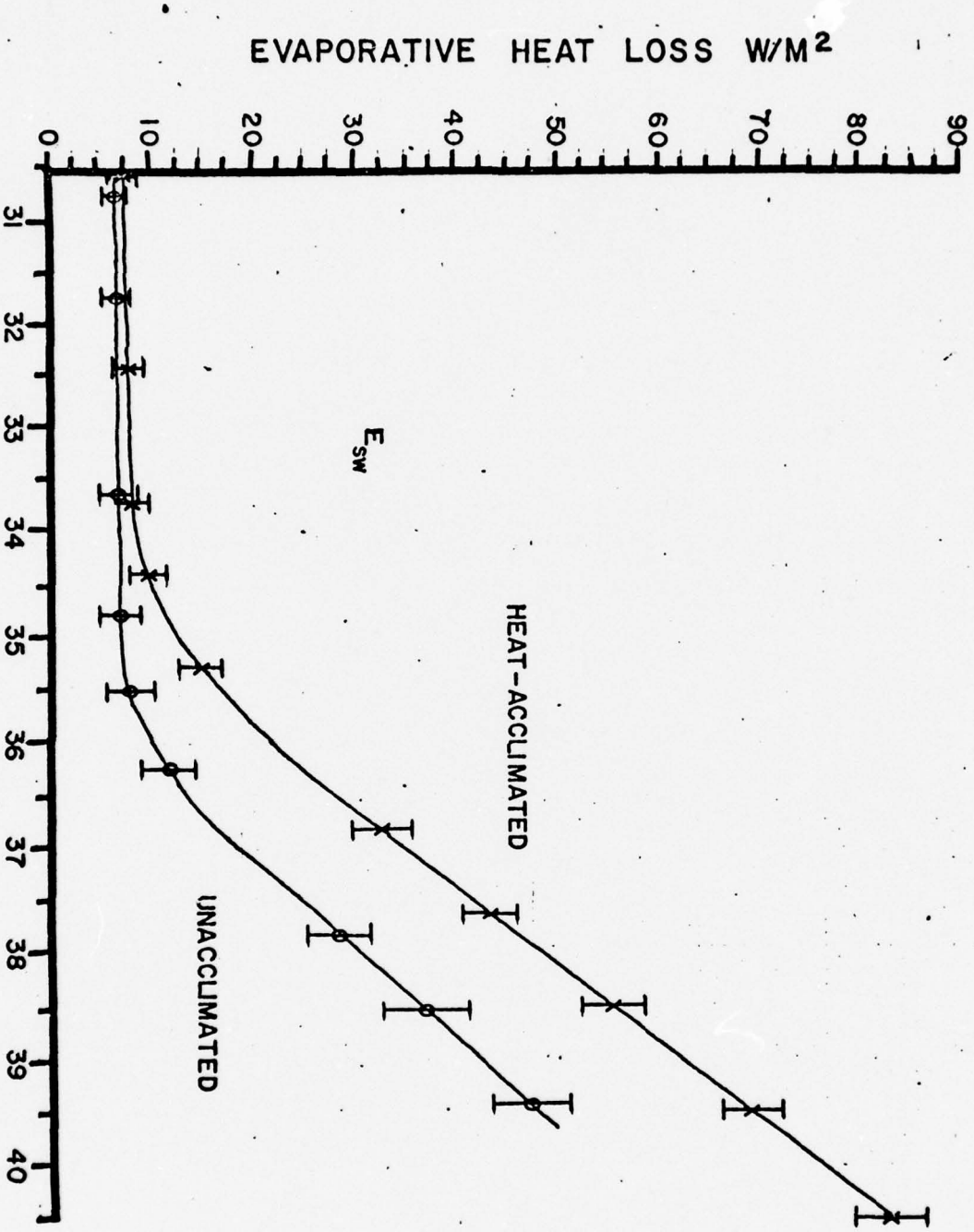
EVAPORATIVE HEAT LOSS W/M2
0
10
20
30
40
50
60
70
80
90
31
32
33
34
35
36
37
38
39
40
MEAN SKIN TEMPERATURE °C
Esw
HEAT-ACCLIMATED
UNACCLIMATED

Figure 23

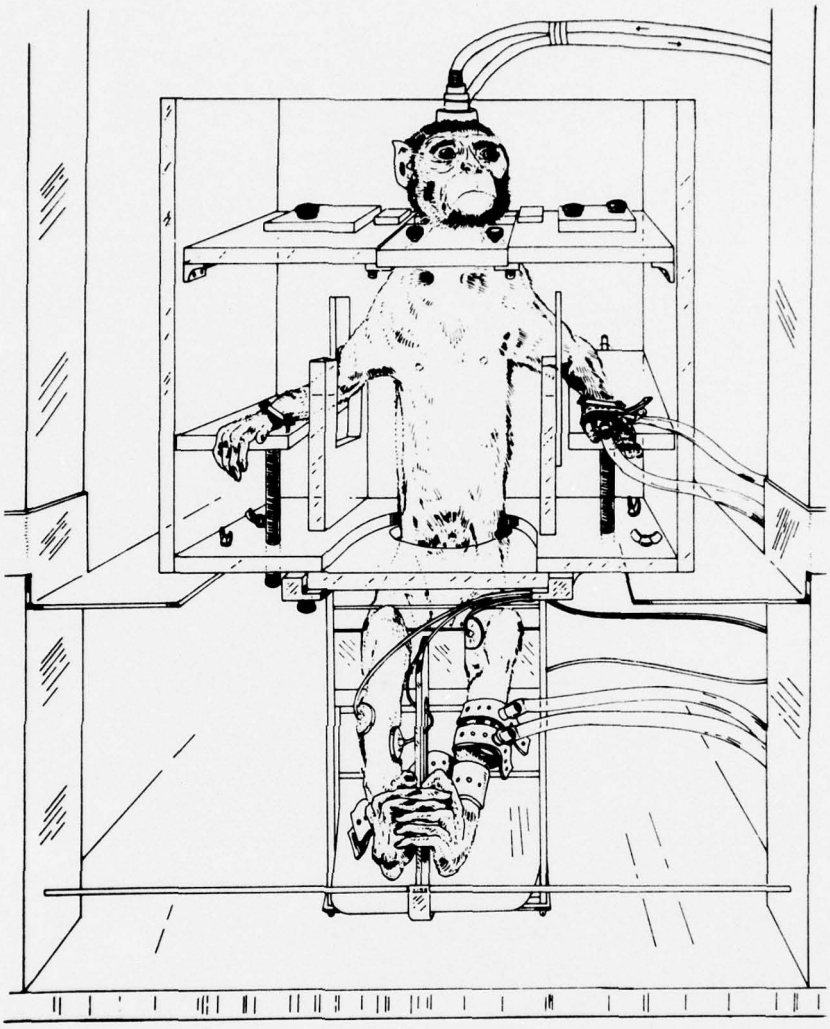

Figure 24

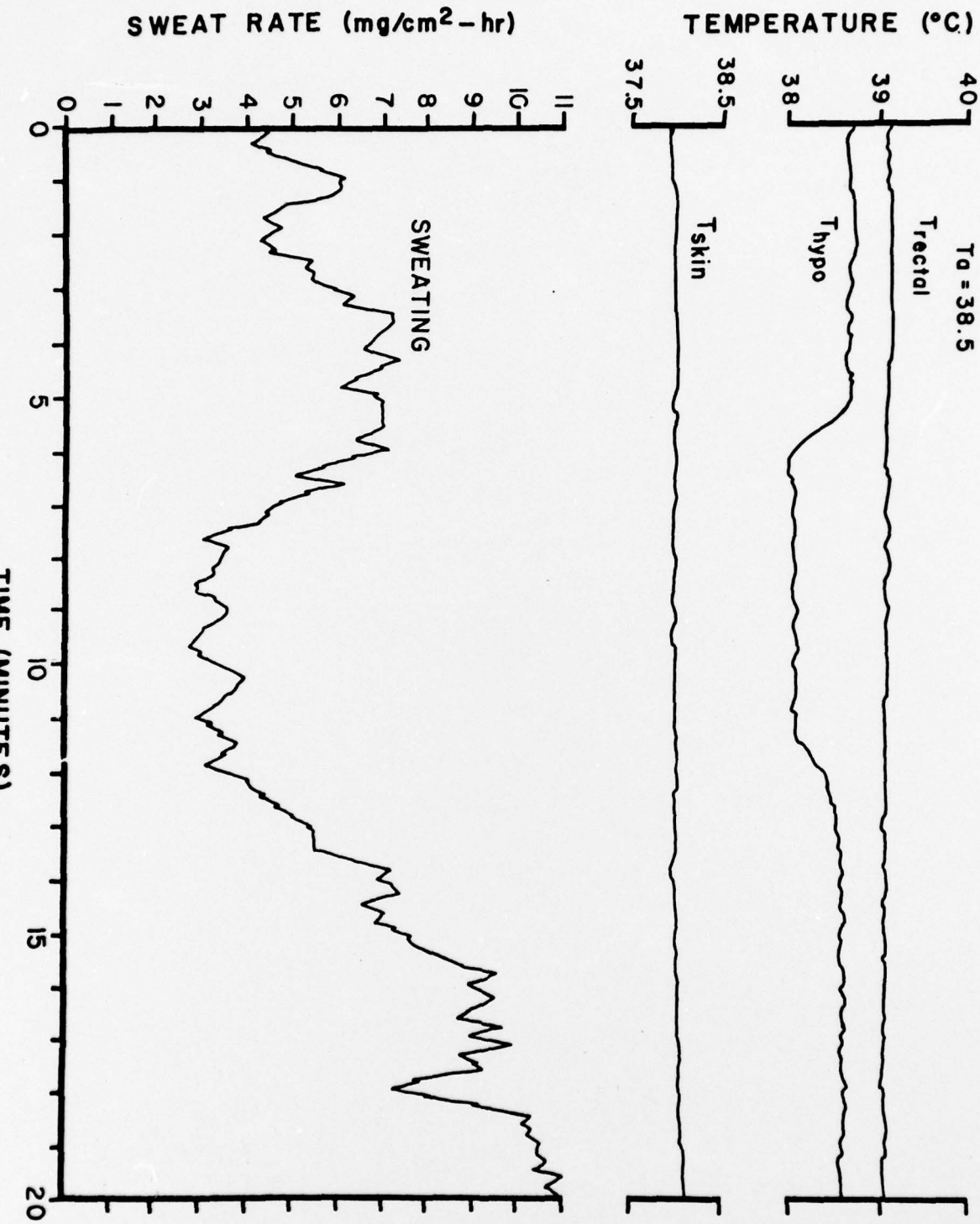
SWEAT RATE (mg/cm²-hr)
TEMPERATURE (°C)
40
39
38
38.5
37.5
Ta = 38.5
Trectal
Thypo
Tskin
SWEATING
0
1
2
3
4
5
6
7
8
9
10
11
0
5
10
15
20
TIME (MINUTES)

Figure 25

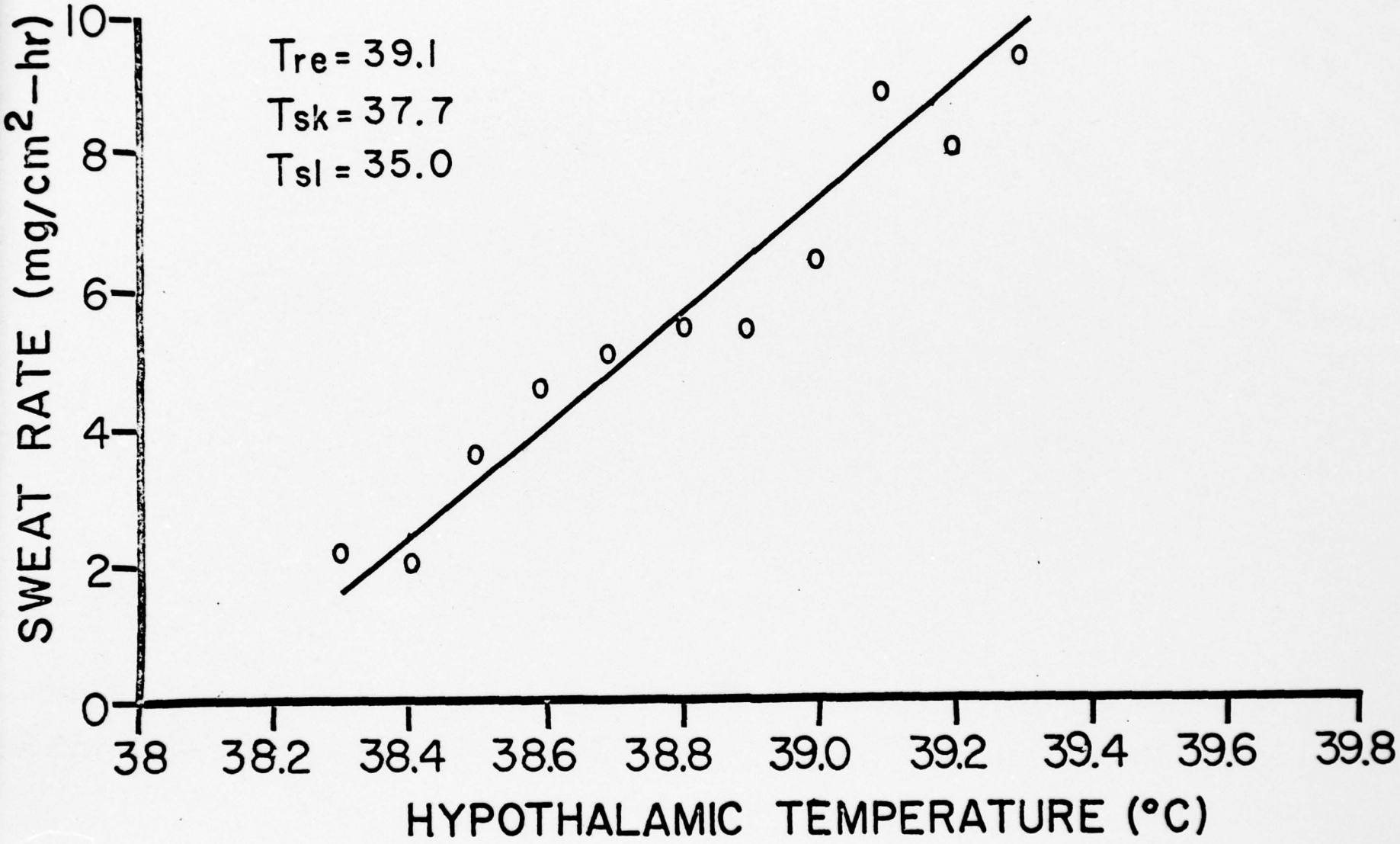
Tre = 39.1
Tsk = 37.7
Tsl = 35.0
SWEAT RATE (mg/cm2–hr)
0
2
4
6
8
10
38
38.2
38.4
38.6
38.8
39.0
39.2
39.4
39.6
39.8
HYPOTHALAMIC TEMPERATURE (°C)

Figure 26

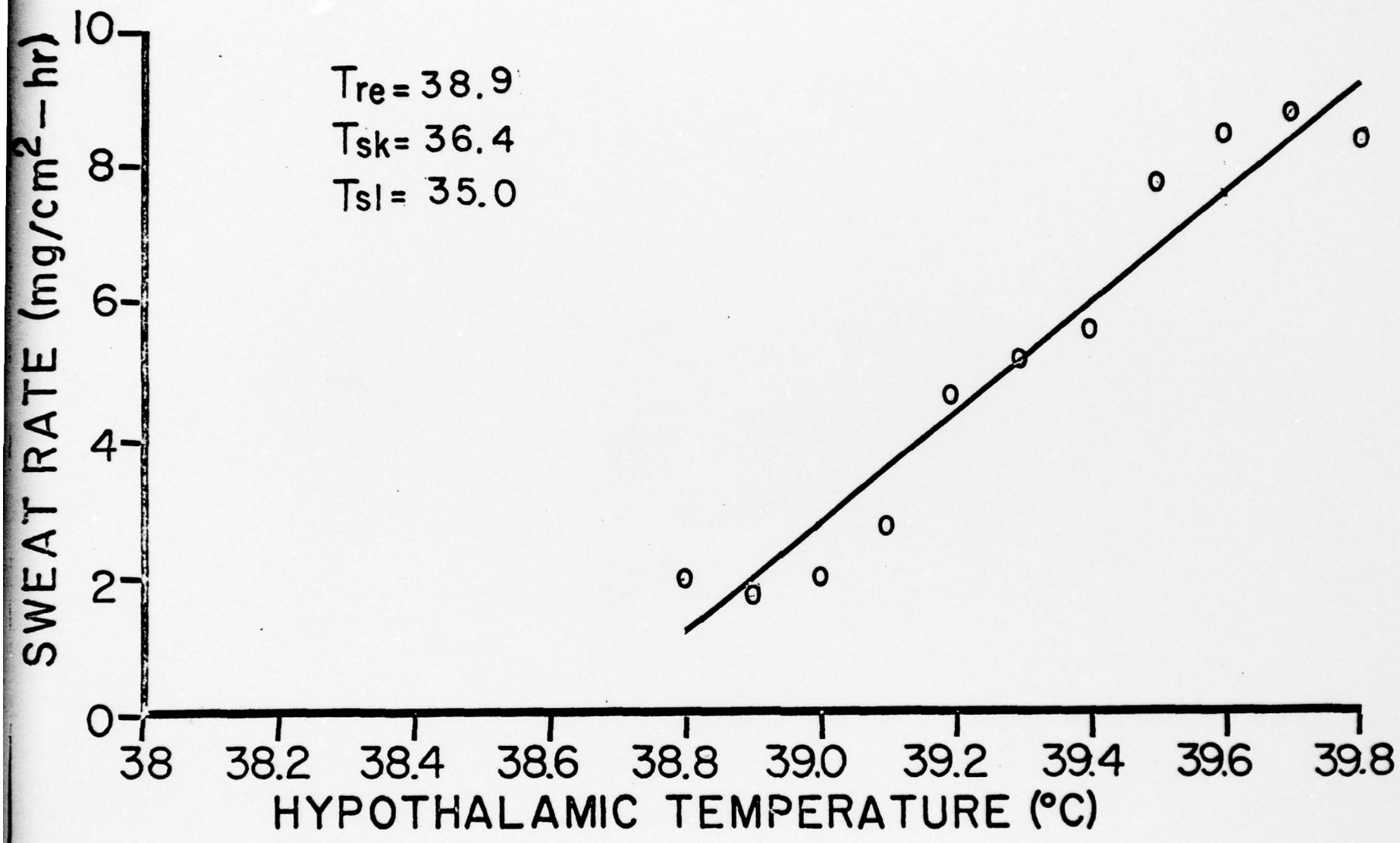
Tre = 38.9
Tsk = 36.4
Tsl = 35.0
SWEAT RATE (mg/cm²–hr)
0
2
4
6
8
10
38
38.2
38.4
38.6
38.8
39.0
39.2
39.4
39.6
39.8
HYPOTHALAMIC TEMPERATURE (°C)

Figure 27

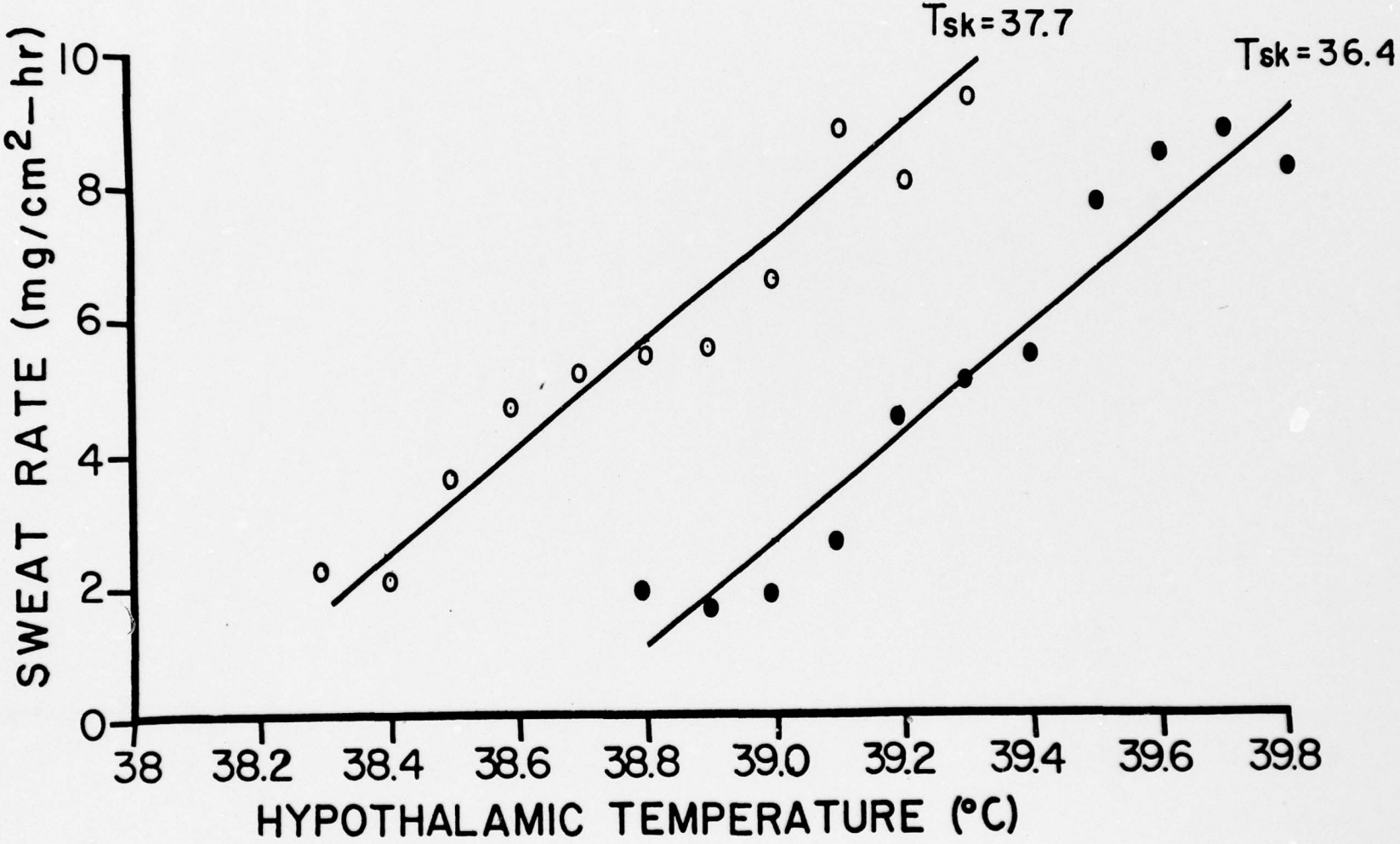
Tsk=37.7
Tsk=36.4
SWEAT RATE (mg/cm2–hr)
0
2
4
6
8
10
38
38.2
38.4
38.6
38.8
39.0
39.2
39.4
39.6
39.8
HYPOTHALAMIC TEMPERATURE (°C)

Figure 28

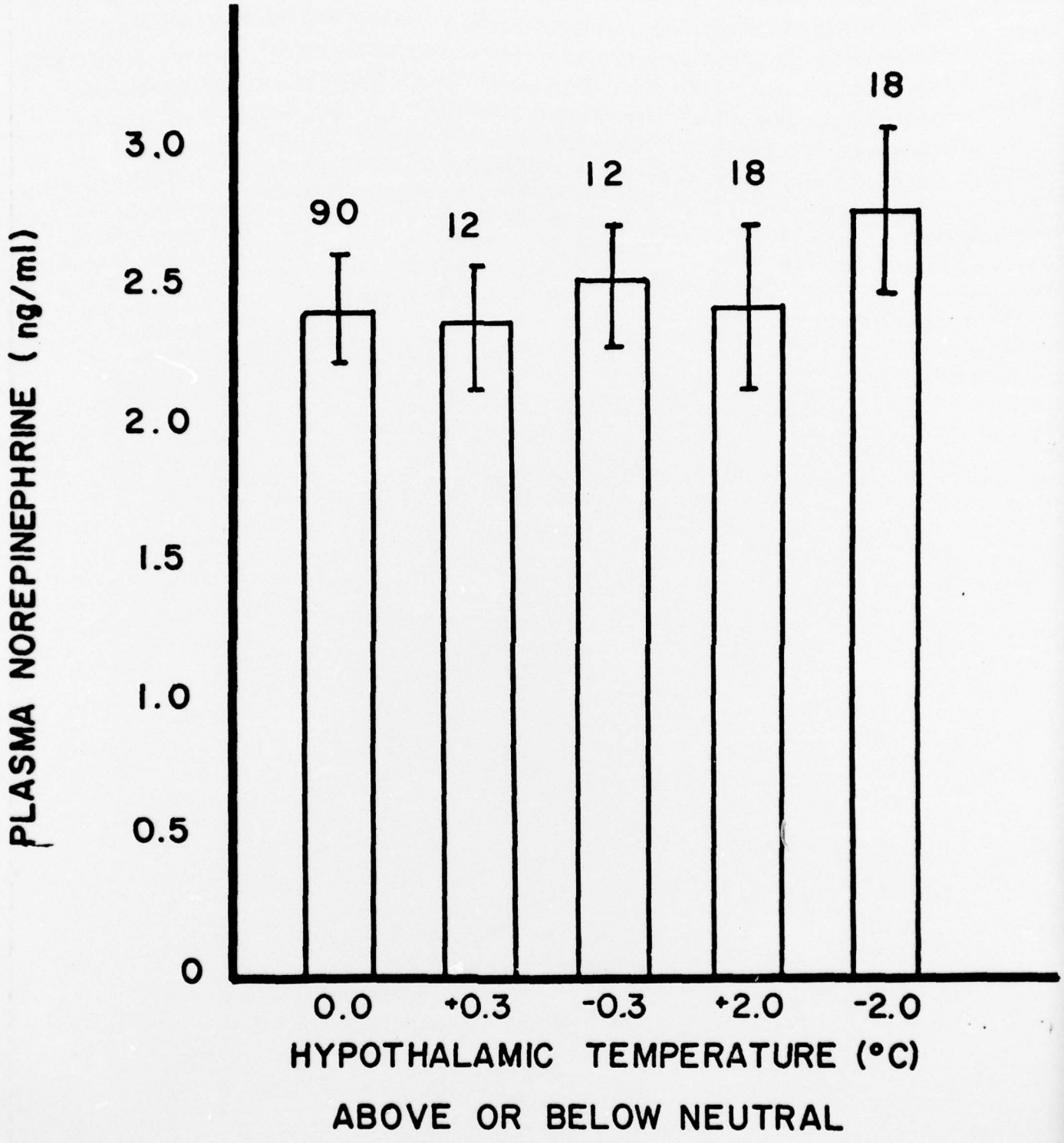
PLASMA NOREPINEPHRINE (ng/ml)
3.0
2.5
2.0
1.5
1.0
0.5
0
90
12
12
18
18
0.0
+0.3
-0.3
+2.0
-2.0
HYPOTHALAMIC TEMPERATURE (°C)
ABOVE OR BELOW NEUTRAL

Figure 29

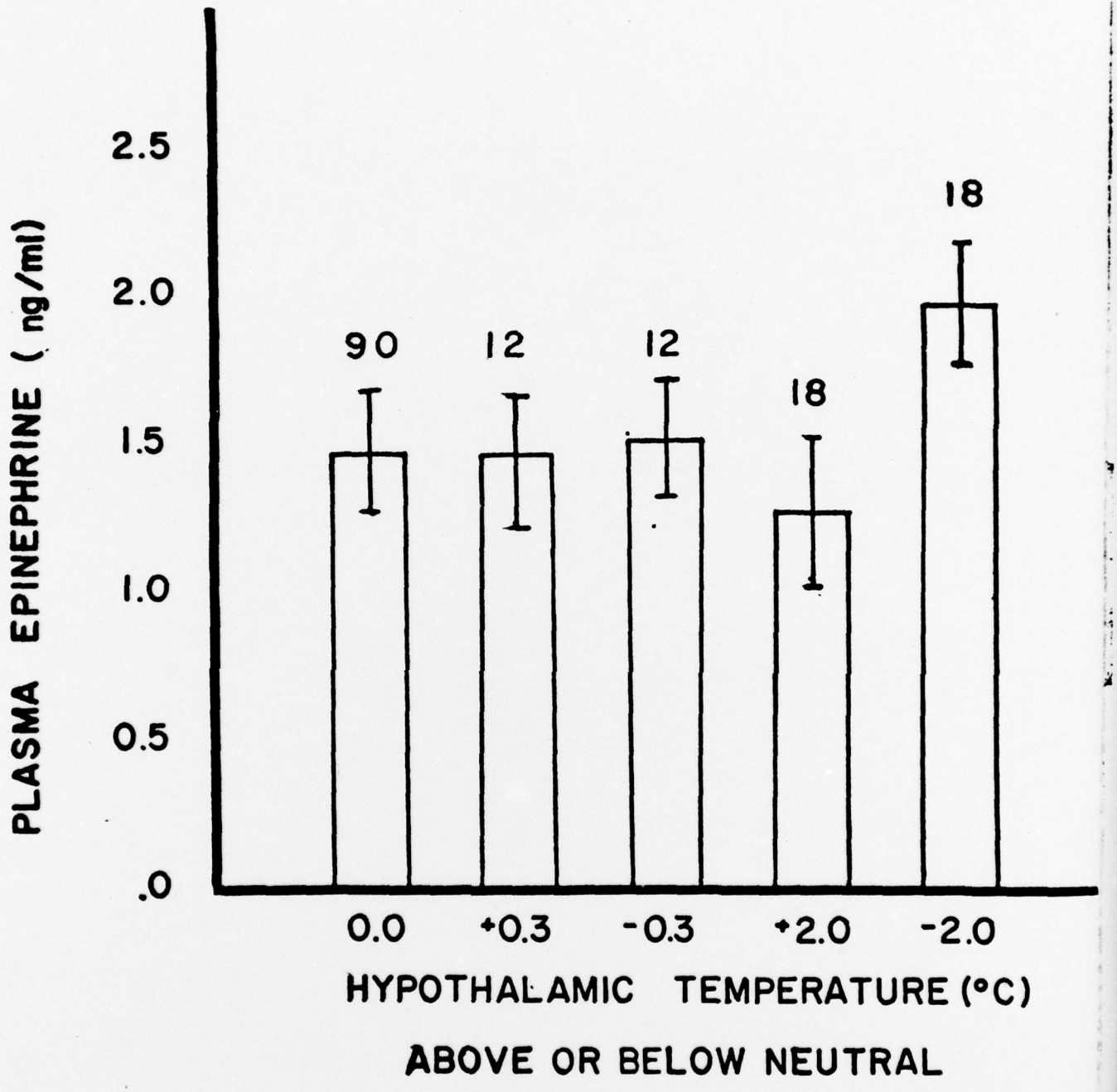
PLASMA EPINEPHRINE (ng/ml)
2.5
2.0
1.5
1.0
0.5
.0
9 0
12
12
18
18
0.0
+0.3
-0.3
+2.0
-2.0
HYPOTHALAMIC TEMPERATURE (°C)
ABOVE OR BELOW NEUTRAL

Figure 30

11. Complete thermalbalance data and development of control systems models for regulation of sweating and metabolic rate in cold acclimated rhesus monkeys. The present study was undertaken to construct a complete thermoregulatory profile of Macaca mulatta before and after cold acclimation. Particular emphasis has been placed on: (a) evaluation of the relative significance of evaporative heat losses due to eccrine sweating (E_{sw}) and respiratory evaporative water loss (E_{resp}), and (b) elucidation of physiological mechanisms for the control of eccrine sweating and metabolic heat production.

A complete thermal balance study using indirect calorimetry was performed on four male, unanesthetized rhesus monkeys (Macaca mulatta), weighing 3.1 - 5.4 kg. over an ambient temperature (T_a) range of 11 - 40°C before and after cold acclimation to 6°C for 4 - 6 weeks. O_2 consumption, CO_2 production, mean-weighted skin temperature ($\bar{T}_s$), rectal temperature (T_{re}), respiratory evaporative water loss (E_{resp}), and total evaporative water loss (E_{tot}) were measured after equilibration at each of 12 successive T_a's as previously described in this report.

Figure 31 shows the relationship between metabolic heat production (M) and ambient temperature (T_a). On this and subsequent figures, open circles represent the unacclimated state, and X's the cold acclimated state; each symbol represents the mean of four animals, ± 2 standard deviations. After cold acclimation, M is significantly elevated ($p < 0.05$) an average of 29% over the range of T_a's employed. As determined by the intercept method of Scholander, the lower critical temperature (LCT) for the increase in M, decreased significantly ($p < 0.05$) from 24.8°C to 23.6°C after cold acclimation. Above the LCT, M increased progressively so that at 15°C it was 1.6 times neutral values after acclimation compared to 1.7 times for control. There are significant negative linear correlations between decreasing T_a and M below the LCT. The elevation in metabolic heat production in the rhesus monkey after cold acclimation is probably due to increased nonshivering thermogenesis (NST). The $\bar{T}_s$ and T_{re} at the LCT increased significantly ($p < .05$) from 33.5 to 35.2°C and 38.1 to 39.0°C respectively, after acclimation.

Attempts at modeling metabolic heat production (M) as a linear additive function of T_{re} and $\bar{T}_s$ were unsuccessful. The physiological control of metabolic heat production in the rhesus monkey appears to follow a multiplicative type of regulation as is the case in man and other mammals such as the cat and rabbit. Figure 32 represents a plot of experimentally determined M versus predicted M derived from a multiplicative function of T_{re} and $\bar{T}_s$ for control animals ($M = 38.7\ (T_{re} - 38.1)\ (\bar{T}_s - 33.5) + 57.2\ W/M^2$). The solid line is the least squares regression line, and the dotted line is the line of equality which would result if this model were an exact predictor of M. Analysis of goodness of fit of the model indicated statistical significance ($p < .01$), and that a predictive model has been obtained.

Figure 33 represents a plot of experimentally determined M versus predicted M for the cold-acclimated animals. Analysis of goodness of fit shows a statistically significant predictive model has been obtained ($p < 0.01$). ($M = 43.5\ (T_{re} - 39.0)\ (\bar{T}_s - 35.2) + 78.2\ W/M^2$)

Figure 34 depicts the relationship between evaporative heat losses due to eccrine sweating (E_{sw}), respiratory water loss (E_{resp}), and T_a.

After cold acclimation, E_{evap} is elevated by an average of 29.2% over the range of T_a's employed, presumably secondary to the increase in internal heat load. As determined by the intercept method, the upper critical temperature (UCT) for the increase in E_{sw} decreased significantly ($p < .05$) from 30.5 to 29.4°C. Consequently, after cold acclimation the thermoneutral zone (TNZ) has shifted downward significantly (from 24.8 to 30.5°C for control to 23.6 to 29.4°C). In the TNZ, sensible water loss (E_{ins}) increased significantly from 12.8 ± 1.1 to 19.5 ± 1.6 W/M^2; there was no change in maximum eccrine sweating (E_{max}) (49.4 to 50.9 ± 4.2 W/M^2) at 40°C: however decreased heat tolerance is partially attributable to the fact that significantly less of M can be dissipated at 40°C by E_{sw} after cold-acclimation (75/74.5% compared to 90/89.7% for control). It should be noted that E_{resp}) is relatively constant and insignificant relative to E_{sw} over the range of T_a's employed.

After cold acclimation E_{resp} is elevated significantly ($p < .05$) by an average of 50.7% over the range of T_a's used; this elevation is presumably secondary to the increased metabolic heat load. If the TNZ, E_{resp} increased from 2.3 ± 0.15 to 3.8 ± 0.24 W/M^2, and at 40°C equal 7.0 ± 0.74 compared to 5.0 ± 0.53 W/M^2 for control. Consequently, it is apparent that E_{sw} serves as the major avenue of heat loss above the UCT in the rhesus monkey.

Figure 35 illustrates a composite plot of mean sweat rate (E_{sw}) before and after cold-acclimation versus mean rectal temperature (T_{re}). In both cases, there are significant linear correlations ($r = 0.99$; $r' = 0.98$) between E_{sw} and T_{re}. After cold acclimation, there is a significant increase ($p < .05$) in the threshold T_{re} for the onset of sweating from 38.0 to 38.3°C, and a significant decrease ($p < .05$) in the gain of the E_{sw}/T_{re} relationship. (24.0 ± 0.5 to 17.6 ± 0.4 $W/M^2 \cdot °C$)

Figure 36 demonstrates a composite plot of mean sweat rate (E_{sw}) before and after cold-acclimation versus mean skin temperature ($\bar{T}_s$). In both cases, there are significant linear correlations ($r = 0.98$; $r' = 0.99$) between E_{sw} and $\bar{T}_s$. After cold acclimation, there is a significant increase ($p < .05$) in the threshold $\bar{T}_s$ for the onset of sweating from 34.9 to 36.1°C, and no significant change in the gain of the $E_{sw}/\bar{T}_s$ relationship.

Figure 37 shows a plot of experimentally determined E_{sw} versus predicted E_{sw} calculated from an expression derived from two parameter regression analysis of T_{re} and $\bar{T}_s$ on E_{sw} for the unacclimated state; where 12.3 and 5.2 are the T_{re} and $\bar{T}_s$ proportional control constants, and 38.0 and 34.9°C are the experimentally determined thresholds for the onset of E_{sw} for T_{re} and $\bar{T}_s$, respectively. The dashed line is the line of equality which would result if the combination of T_{re} and $\bar{T}_s$ were exact predictors of E_{sw}: the solid line is the least squares regression line for the data. For a resting monkey in a steady state, the data points distribute well with respect to the predicted line. The relative weighting of the T_{re} to $\bar{T}_s$ proportional control constant is 2.37:1 for the non-acclimated, resting rhesus monkey.

Figure 38 illustrates a plot of experimentally determined E_{sw} for the cold-acclimated animals versus predicted E_{sw} derived from regression analysis as in the previous slide, where 9.0 and 5.2 are the T_{re} and $\bar{T}_s$, proportional control constants, respectively, and 38.3 and 36.1°C are the experimentally determined thresholds for the onset of E_{sw} for T_{re} and $\bar{T}_s$, respectively. The relative weighting of the T_{re} to $\bar{T}_s$ proportional control constants is

1.73 as compared to 2.37 for the non-acclimated animals.

Figure 39 illustrates a comparison of models describing the physiological control of eccrine sweating on the whole body before and after cold-acclimation. After cold-acclimation there is: (1) a significant increase ($p < .05$) in the thresholds for the onset of sweating in terms of T_{re} and $\bar{T}_s$ (i.e., 0.3 and 1.1°C, respectively. (2) a significant decrease in the relative weighting of the T_{re} and $\bar{T}_s$ proportional control constants, i.e., a/B of 2.37 to 1.73. (3) a significant decrease (p .05) in the T_{re} proportional control constants as indicated by a'/a being 0.73; and (4) no significant change in the $\bar{T}_s$ proportional control constant with the relative change as indicated by B'/B being 1.00. Consequently, cold acclimation in Macaca mulatta results in a significant increase in the input from the periphery to the central controller (hypothalamus) relative to the input from the core as regards the drive (or forcing) for the sweating response.

In summary, these data suggest that cold-acclimation in Macaca mulatta is characterized by: (1) increased resting M throughout the range of T_a's employed attributable to increased non-shivering thermogenesis (NST); (2) a downward shift in the TNZ; (3) an increase in the T_{re} and $\bar{T}_s$ thresholds for the onset of E_{sw} (of 0.3 and 1.1°C respectively); no change in the gain of the E_{sw}/T_{re} relationship; and no change in maximal sweating capacity (E_{max}; from 36.6 + 4.2 to 31.4 + 4.1 W/M^2; (4) decrease in the sensitivity of the regulation of sweat rate by the central controller with the relative input from the periphery being more important than that from the core; and (5) decreased heat tolerance.

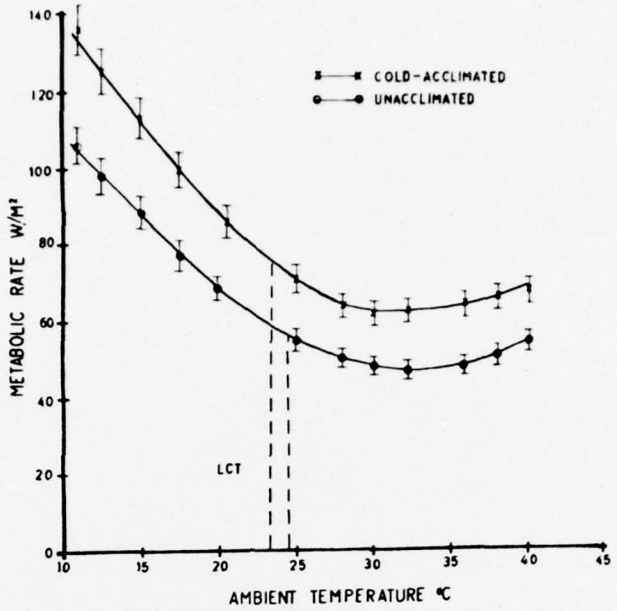

Figure 31

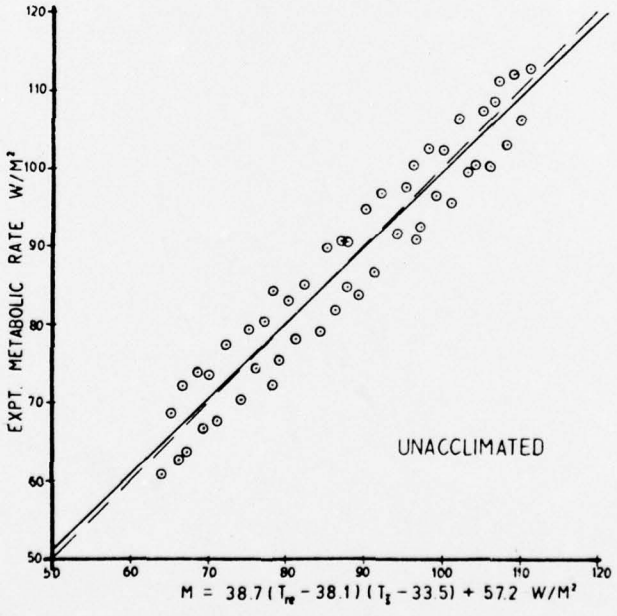

Figure 32

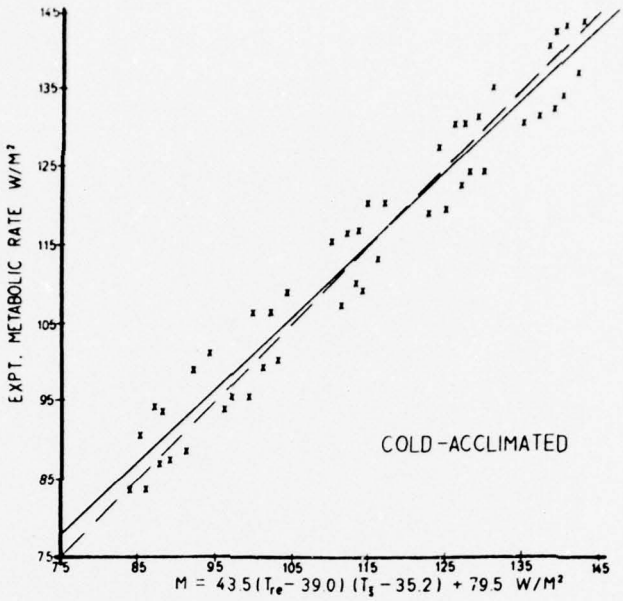

Figure 33

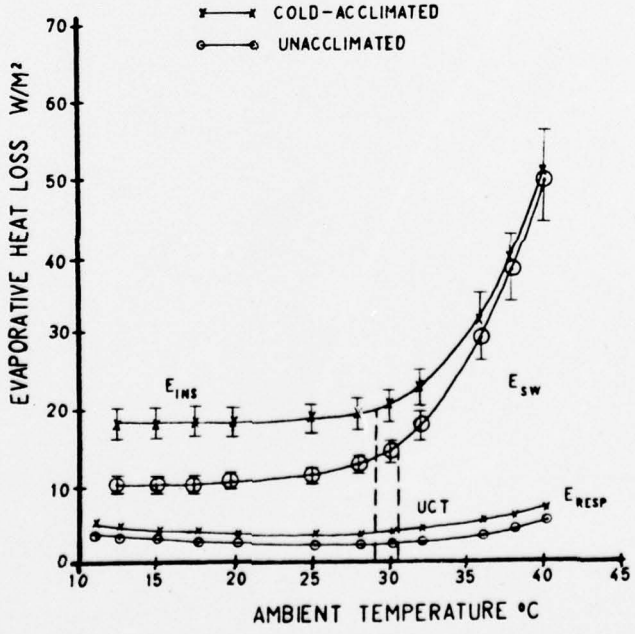

Figure 34

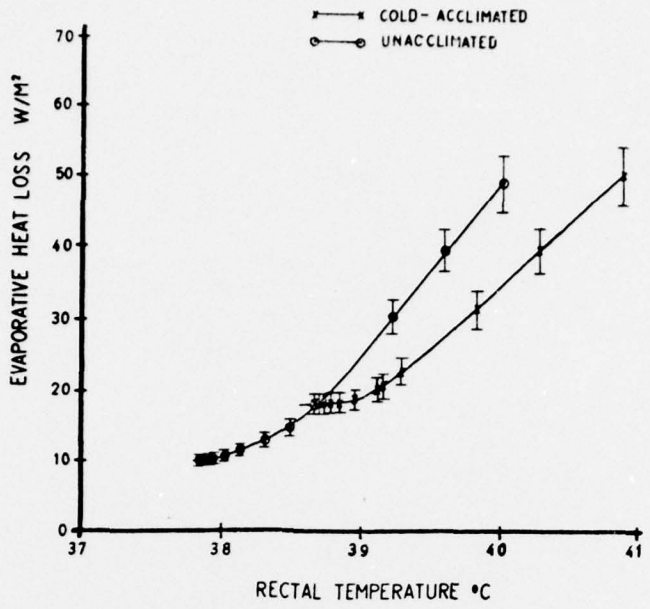

Figure 35

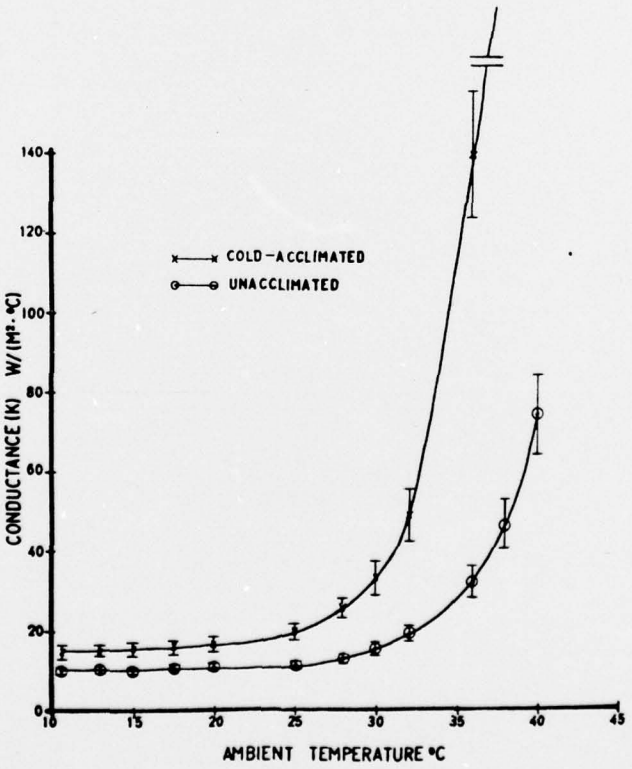

Figure 36

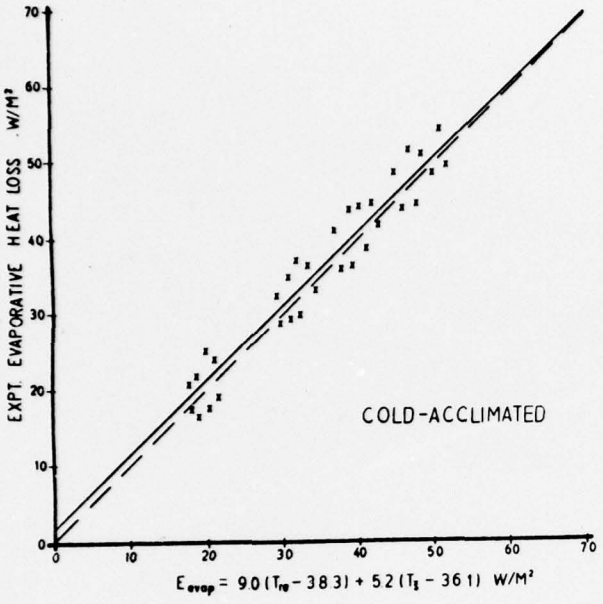

Figure 37

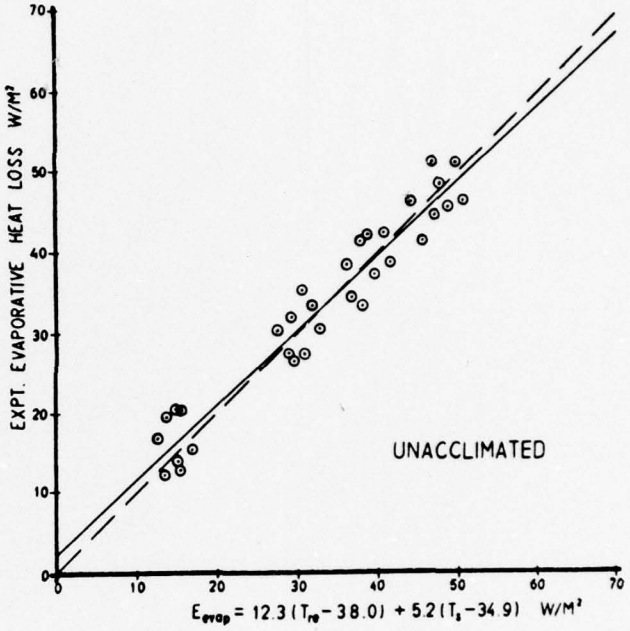

Figure 38

Multiplicative models of metabolic heat production

GENERAL FORM:

$$M_{(unaccl.)} = a(Tre - Tre_o)(Ts - Ts_o) + M_o \quad W/M^2$$

$$M'_{(accl.)} = a'(Tre - Tre'_o)(Ts - Ts'_o) = M'_o \quad W/M^2$$

	$a(')$ $(W/(M^2 \cdot {}^oC^2))$	$Tre_o(')$ $({}^oC)$	$Ts_o(')$ $({}^oC)$	$M_o(')$ (W/M^2)
UNACCL:	38.7	38.1	33.5	57.2
COLD-ACCL:	43.5	39.0	35.2	78.2

Figure 39